ACUTE HAEMODYNAMIC EFFECTS OF A NEW CALCIUM ANTAGONIST, NICARDIPINE, IN MAN. A COMPARISON WITH NIFEDIPINE

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1 The acute cardiovascular response to nicardipine was investigated using non invasive techniques in normal subjects.

2 In six subjects, i.v. nicardipine in an increasing dose (0.5–20 mg) was compared with saline, under double-blind conditions. A dose related increase in heart rate and fall in blood pressure were found. Pre-ejection period (PEP) and PEP/left ventricular ejection time (LVET) ratio of the systolic time intervals were shortened in a clearly dose related manner. Total electromechanical systole index (QS₂ I) was decreased and LVET index prolonged.

3 In four subjects increasing oral doses (10–40 mg) of nicardipine, administered in a randomized double-blind placebo control design, demonstrated the same pattern, marked changes being found with the 40 mg dose.

4 Comparison with nifedipine in a double-blind-placebo controlled balanced trial in six subjects confirmed that 40 mg nicardipine and 20 mg nifedipine exhibited similar effects. Maximum response was reached between 0.5 and 1.5 h, and changes in some cardiovascular variables were still evident at 3 h.

Introduction

Nicardipine, ($\pm$ 2, 6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2-*N*-benzyl *N*-methylamino ethyl ester 5-methyl ester hydrochloride) is a new calcium antagonist (slow channel blocker) effective in animals and man (Bowles *et al.*, 1982; Ahuja *et al.*, 1982). Calcium antagonists inhibit the influx of calcium ions across cell membranes—particularly in myocardium and vascular smooth muscle—by blocking the slow inward calcium channel. They favour relaxation and diminish smooth muscle contractility which results in coronary and systemic vasodilatation. In the intact organism these actions are modified by compensatory reactions of the baroreceptor system.

Calcium antagonists have attracted particular attention in the treatment of angina pectoris and hypertension. Hagemann *et al.* (1975) attributed their beneficial effects to a reduction in left ventricular pre-load and after-load, while others have claimed that their anti-anginal effects depend on their ability to augment cardiac output by increasing venous return (Ludbrook *et al.*, 1982). Despite a demonstrable negative inotropic effect *in vitro* the influence of these drugs on systolic and diastolic left ventricular performance *in vivo* remains controversial (Rousseau *et al.*, 1980; Ludbrook *et al.*, 1980; Amende *et al.*, 1980). The present study was undertaken to define

the dose of nicardipine which produces detectable haemodynamic effects, and to characterise the drug's actions on left ventricular systolic performance and BP in normal subjects at rest, using non-invasive methods. The design enabled us to investigate the magnitude and time course of these effects and to compare them with those of nifedipine.

Methods

Sixteen non-smokers, aged 19–37 years with normal ECG and healthy on the basis of medical history and physical examination, took part in these studies. All subjects gave written informed consent for the study which was approved by the Ethical Committee of St Bartholomew's Hospital. They refrained from other drug treatment throughout the study period (2 weeks) and were fasting overnight before the study days and during the test period which started at 09.00 h. They lay on a couch during the study period (0.5–3 h). They were asked to volunteer any possible side effects.

The studies were of double-blind, placebo-controlled, cross-over type, with each subject serving as his own control. A 3 day wash-out interval was allowed between treatments.

Preliminary studies

Six subjects (group 1), four males and two females (weight 59–75 kg) received two i.v. treatments: one of the following doses, 0.5, 1, 2, 5, 10 or 20 mg of nicardipine, and equivalent volume saline placebo. Each treatment was given as a 25 ml infusion over 5 min using a constant infusion syringe pump prepared by a second, independent investigator immediately before administration. Doses up to 5 mg were given in a randomised way but higher doses were administered in an incremental manner. Systolic time intervals (STI), ECG lead II resting heart rate (HR) and supine blood pressure (BP) were recorded before (control), at the end of the infusion (0 min), 5, 10, 20 and 30 min after the infusion. Erect BP was measured from 10 min onwards to avoid disturbing the STI recordings.

Four further subjects (group 2), two of each sex (weight 52–61 kg) received two oral treatments: one of the following 10, 15, 20 or 40 mg dose of nicardipine, and matching placebo in a randomised trial. STI, ECG lead II, and supine and erect BP recordings were performed before drug administration and every 30 min for 3 h.

Comparison of nicardipine, nifedipine and placebo

Six male subjects (group 3), (weight 62–81 kg) were given three oral treatments, 40 mg nicardipine, 20 mg nifedipine and matching placebo in a balanced design. Recordings (as above) were carried out before and at 0.5, 1, 1.5, 2, 2.5 and 3 h after drug administration.

STI and ECG (lead II) were recorded as described (Burgess *et al.*, 1978) on a three channel ink-jet recorder (Nihon Kohden, Japan) at 100 mm/s paper speed, taking at least 10 cardiac cycles and averaging the results. BP was measured using the London School of Hygiene sphygmomanometer in the supine position and after 2 min standing. Resting HR was measured from the ECG. The tracings were analysed 'blind' by a single investigator. Measured values were corrected for changes in heart rate using regression equations (Burgess *et al.*, 1979):

$$\begin{aligned}\text{male: } \text{QS}_2\text{-I} &= \text{QS}_2 + (1.2 \times \text{HR}) \\ \text{LVET-I} &= \text{LVET} + (1.1 \times \text{HR})\end{aligned}$$

$$\begin{aligned}\text{female: } \text{QS}_2\text{-I} &= \text{QS}_2 + (1.6 \times \text{HR}) \\ \text{LVET-I} &= \text{LVET} + (1.5 \times \text{HR})\end{aligned}$$

$$\begin{aligned}\text{male + female QT-I} &= \text{QT} + (1.7 \times \text{HR}) \\ &(\text{Bryson } et al., 1978)\end{aligned}$$

The significance of differences between the three treatments in group 3 was tested using parametric analysis of variance with a critical value $P = 0.05$. Because of the limited number of subjects in the preliminary studies, the values of the differences from

control were tested against the placebo differences from control, at 1% level of significance (for group 1). No statistical test was applicable to the results from group 2.

Results

Preliminary studies

Group 1 The results for BP, HR and STI for individual subjects of group 1, who received increasing intravenous doses of nicardipine, and saline, are presented in Figure 1. Supine BP showed a significant dose related decrease, more evident in the diastolic component, with doses of 5 mg or greater. Maximum fall from control value was 18% in the systolic and 72% in the diastolic with the 20 mg dose. Erect BP was less affected at low doses, but postural hypotension occurred with the 20 mg dose. HR demonstrated a significant dose related increase, reaching a maximum of 59% at the end of the 20 mg infusion. $\text{QS}_2\text{-I}$ was significantly shortened by 1, 5 and 20 mg. A maximum change of 6.5% from control occurred at 20 min after administration of 20 mg. LVET-I was prolonged by nicardipine, although with 0.5 and 1 mg doses it tended to decrease. Maximum prolongation of 9% from control values occurred at the end of the infusion. PEP was significantly shortened in a clearly dose related manner, with a maximum decrease of 51% at 20 min after the 20 mg dose. PEP/LVET ratio was also decreased with increasing dosage.

No significant differences in the ECG complexes and intervals (PR, QRS, QT-I) were observed. However, T wave amplitude was clearly reduced when dosage was 2 mg or more.

Group 2 The results for BP, HR and STI measured in the four subjects of group 2 treated with increasing oral doses of nicardipine are shown in Figure 2. Supine and erect diastolic BP were consistently decreased only by the highest dose but no clear effect on systolic BP was observed. $\text{QS}_2\text{-I}$ and PEP and PEP/LVET were shortened in a dose-related fashion after the two highest doses.

LVET-I was prolonged at early times with most doses but only with the highest did the effect last up to 1.5 h. Most of the changes reached a peak between 0.5 and 1.5 h after administration and some were still present at 3 h (see Figure 2).

Comparison of nicardipine, nifedipine and placebo

The mean ($\pm$ s.e. mean) values for BP, HR and STI of the six subjects of group 3 who received nicardipine, nifedipine and placebo are presented in Figures 3 and 4.

Figure 1 Effect of increasing intravenous doses of nicardipine and saline on BP, HR, total electromechanical systole index (QS_2-I), left ventricular ejection time index (LVET-I), pre-ejection period (PEP) and PEP/LVET ratio. Each column represents results from individual normal subjects in Group 1. INF = infusion period, C = control value. — nicardipine, ---- saline.

Figure 2 Effect of increasing oral doses of nicardipine and placebo on BP, HR, total electrochemical systole index (QS₂₋₁), left ventricular ejection time index (LVET-I) pre-ejection period (PEP) and PEP/LVET ratio. Each column represents results from individual normal subjects in Group 2. — nicardipine, --- placebo.

Figure 3 Mean $\pm$ s.e. mean values of (S) systolic and (D) diastolic blood pressure in six normotensive subjects (Group 3) after oral administration of nicardipine 40 mg, nifedipine 20 mg, and placebo. (Asterisks indicate values significantly different from placebo after both active treatments. * = $P < 0.05$, ** = $P < 0.01$). — nicardipine, - - - nifedipine, . . . placebo.

Mean supine systolic and diastolic BP tended to fall for both drugs with the systolic component reaching significance at 1.5 h. There was a bigger reduction in the erect BP for both active treatments, reaching significance at 1 h in systolic and diastolic pressures and at 2 h in the systolic only. There were maximum systolic falls of 8% and 10% for nifedipine and nicardipine respectively, and maximum diastolic falls of 9.6% and 14.6% for nifedipine and nicardipine respectively.

Mean heart rate was increased for both treatments compared with placebo being significant between 0.5 h and 1.5 h. The biggest increase was at the 0.5 h recording (15.9% and 12.3% from control for nifedipine and nicardipine respectively).

There was a significant fall in QS_2 -I values after both treatments compared with placebo from 0.5 to

Figure 4 Mean $\pm$ s.e. mean values of HR, total electro-mechanical systole index (QS_2 -I), left ventricular ejection time index (LVET-I), pre-ejection period (PEP) and PEP/LVET ratio in six normal subjects (Group 3) after oral nicardipine 40 mg, nifedipine 20 mg, and placebo. (Asterisks indicate values significantly different from placebo after both active treatments. * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$).

1.5 h following drug administration. The greatest difference, 1.7% from control, was with nicardipine.

After both drugs, values of LVET-I increased and returned to control level at 3 h. The differences from placebo were just greater than 2.5% for both drugs, and were significant at 0.5 and 1 h recordings. Mean PEP was shortened significantly from 0.5 to 2 h with changes still detectable at 3 h for nifedipine and

nicardipine. The biggest reduction, 15.4% from control, was observed with nicardipine.

At the same times mean PEP/LVET ratio values were decreased, following a similar pattern to PEP. Differences from placebo were significant at 0.5, 1 and 1.5 h with 16.1% and 16.6% the highest differences from control for nifedipine and nicardipine respectively.

No significant changes were found in PR interval, QRS complex duration and QT-I values of the ECG between the three treatments. Although mean T wave amplitude values were decreased by both active drugs up to 2 h, the changes were not significant.

Side effects

Observed side effects were:

Group 1 (i.v. study—slight headache in the three subjects who received doses of 5 mg or greater, and postural hypotension and sinus tachycardia 100 beats/min after the 20 mg dose of nicardipine.

Group 2—slight headache (one subject).

Group 3—slight headache after nicardipine (two subjects) and after nifedipine (two subjects) but also after placebo (two of the above four)—facial flushing after both active treatments (one subject of each).

Discussion

The results from the present studies show that nicardipine has similar haemodynamic effects to nifedipine in normal subjects. The consistent increase in HR by both calcium antagonists is attributable to reflex adrenergic stimulation owing to fall in peripheral resistance. This is compatible with increased catecholamine levels measured after nifedipine administration in normotensive, hypertensive (Lederballe-Pedersen *et al.*, 1980) and heart failure patients (Corea *et al.*, 1981).

The arterial BP reduction following administration of both drugs is the result of a vasodilator effect predominantly on the resistance vessels. Esper *et al.* (1975) and Linke (1975) have reported similar results with nifedipine in normotensive subjects. However Aoki *et al.* (1978) and Lederballe-Pedersen *et al.* (1980) found significant decreases in BP in hypertensive but not in normotensive people after sublingual administration of nifedipine. These discrepancies could be due to different methodology or individual differences in the sensitivity of the baroreceptor reflex mechanism. An optimally operating baroreceptor mechanism maintains the level of BP and increases HR following vasodilation, unless the dilatation is very powerful. A greater reduction in vascular resistance and blood pressure might be expected in hypertensives in whom a decreased baroreceptor sensitivity and increased peripheral

resistance are present. Several authors have reported that cardiac output is increased by calcium blockers (Muracakami *et al.*, 1972; Guazzi *et al.*, 1977; Simonsen & Nitter-Hauge 1978); and it is possible that this increase may counteract their hypotensive effect.

In all studies a clear shortening of QS₂-I by both drugs was observed. This index reflects the inotropic state of the myocardium and its magnitude is inversely related to adrenergic activity. The explanation for the shortening of QS₂-I in these studies is probably reflex adrenergic stimulation occurring in response to vasodilatation.

LVET-I reflects myocardial contractility but is also directly related to stroke volume and inversely related to systemic arterial blood pressure. All the ejection phase indices are sensitive to variations in pre-load and after-load, both of which are changed by calcium channel blockers, and changes in myocardial contractility cannot necessarily be deduced from changes in STI. We assume that the LVET-I increase in our study is mainly the result of increased stroke volume. This is supported by the findings of Sawayama *et al.* (1969) who showed that amyl nitrite, which decreases both pre-load and after-load, shortens LVET-I.

The PEP shortening was the most characteristic effect observed after both drugs in any dose by either route of administration. Reduction in PEP may indicate increased myocardial contractility, reduced after-load, or increased pre-load. In these studies, shortening of PEP was associated with reduction in diastolic pressure, but an additional contribution from increased venous return and reflexly enhanced contractility cannot be excluded. The changes in PEP (and also QS₂-I and LVET-I in these studies are very similar to those seen after oral hydralazine (Barbat *et al.*, 1980), and there is no evidence that hydralazine has any direct action on the myocardium. The PEP/LVET ratio decrease corresponds very closely with the changes in PEP. Although some investigators consider the PEP/LVET ratio to be a very reliable index of contractility and relate it to ejection fraction (Garrard *et al.*, 1970) we believe it simply follows changes in PEP and LVET and cannot be independent of pre-load and after-load.

In conclusion, oral doses of nifedipine 20 mg and nicardipine 40 mg, exerted salutary effects on indices of systolic left ventricular performance, HR and BP in normal subjects at rest without influencing ECG intervals or morphology. No significant difference was found between the drugs although some of nicardipine's effects tended to be larger. For most variables the maximum effect (difference between placebo and drug value) was greatest at the 0.5 h recording falling off after 2 h although the values had not returned to control after 3 h. This indicates a possible duration of action of at least 3 h.

The results of the oral studies confirm those of the preliminary study in which 0.5–20 mg i.v. nicardipine demonstrated clear dose-related effects. Intravenous doses of more than 10 mg should be given with caution, since 20 mg caused postural hypotension.

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