A double-blind randomized cross-over study of the efficacy and tolerability of nifedipine and nitrendipine in the treatment of mild to moderate hypertension

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1 In order to examine whether nitrendipine was superior to slow release nifedipine as monotherapy in the treatment of mild to moderate essential hypertension, the two agents were administered to 22 patients in a double-blind randomized cross-over study, incorporating low and titrated dose regimes.

2 Six patients failed to complete the study because of vasodilator side-effects such as headache, flushing and ankle swelling. Three were taking nitrendipine and three took nifedipine and all withdrawals occurred at the introduction of the drug.

3 Both agents reduced blood pressure in the 16 patients who completed the study, and neither agent was superior to the other; mean blood pressure after the placebo phase was $177 \pm 5.5/100 \pm 2.6$ mm Hg supine and $175 \pm 5.3/113 \pm 2.4$ mm Hg standing. At the end of therapy with nifedipine pressures were $160 \pm 4.0/91 \pm 3.0$ mm Hg supine and $158 \pm 4.6/103 \pm 2.7$ mm Hg standing. After 8 weeks treatment with nitrendipine blood pressures were $162 \pm 4.4/90 \pm 2.9$ mm Hg supine and $161 \pm 6.2/104 \pm 2.7$ mm Hg standing. Comparisons of these attained blood pressures on both agents showed no statistically significant differences.

4 Nitrendipine did not appear to be effective on a once daily basis.

Keywords hypertension calcium antagonists nitrendipine nifedipine

Introduction

The introduction into clinical practice of the dihydropyridine calcium channel antagonist drug nifedipine has provided a novel and effective agent for the treatment of hypertension (Lederballe Pedersen, 1983). However, as with all drugs, compliance is limited by a number of factors such as the incidence of unwanted side-effects and the frequency of administration. The newer dihydropyridine nitrendipine may offer an improved alternative to nifedipine in as much as it can be administered to some patients on a once daily basis (Franz & Wiewel, 1984; Ruddel *et al.*, 1984). Therefore we have compared nitrendipine and nifedipine in the treatment of mild to moderate hypertension in a randomized double-blind cross-over experiment.

Methods

Patients

Patients with mild to moderate essential hypertension were studied, in whom thorough investigations had excluded secondary causes of raised blood pressure. Subjects were considered for inclusion into the study if they were between 18 and 70 years of age and not female of child-bearing potential. Hypertension was defined as blood pressure greater than 160/95 mm Hg in either supine or standing positions and patients were eligible if they met these criteria either if they had received no medication, or if the blood pressure exceeded these levels on three separate occasions after their pre-existing medication was withdrawn; however cessation of treatment was

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Figure 1 Study protocol.

only permitted if patients were experiencing intolerable side-effects on current medication. Patients were considered unsuitable if they had malignant hypertension, systolic pressures greater than 220 mm Hg or diastolic pressures greater than 120 mm Hg, significant renal impairment (defined as serum creatinine $> 150 \mu\text{mol l}^{-1}$) or cardiovascular disease such as unstable angina or recent myocardial infarction. Similarly, anyone who had recently sustained a cerebrovascular accident was excluded. All patients were required to give full informed consent and the study was approved by the local Ethics Committee.

Study design

The study design was a randomized double-blind placebo controlled cross-over approach (Figure 1). Upon recruitment, patients were assigned to take placebo for 2 weeks, in the form of three dummy tablets orally twice daily. At the end of 2 weeks, if the patients still fulfilled the entry criteria, they would proceed to the active phase of the study, for which they were randomized to take either nifedipine or nitrendipine first. Subjects assigned to take nifedipine first took nifedipine retard 20 mg orally twice daily. This was achieved by substituting two of the dummy tablets with nifedipine. Those given nitrendipine first, took nitrendipine 20 mg orally once daily, by having one of the morning dummy tablets changed for active drug. All patients were seen again at week 5. Those who had a target blood pressure of 95 mm Hg diastolic or less in both

supine and standing positions were termed 'responders' and continued upon their current treatment. Those whose blood pressure had failed to fall sufficiently were labelled 'non-responders': such patients taking nifedipine had the dose raised to 40 mg orally twice daily, by having nifedipine substituted for a further dummy tablet in the morning and evening. Those patients taking nitrendipine had the dose increased to 20 mg orally twice daily. All subjects were reassessed at week 8, and switched back to three dummy tablets twice daily for 2 weeks as a 'wash-out' procedure. At week 10, subjects were crossed over to the other therapy, and seen again at weeks 13 and 16, to assess their response to the second treatment. At week 16 the trial was completed.

Parameters measured

At each visit blood pressure was measured after 5 min rest in the supine position using a Hawksley random zero sphygmomanometer. Two readings were taken and the mean value recorded. Standing blood pressure was measured 60 s after rising from the supine position using the same technique. The pulse rate was recorded over 60 s in both positions. In addition, the patients were weighed and upon recruitment and at weeks 8 and 16 venous blood was drawn for urea and electrolytes (U+E), creatinine, glucose, protein, albumin and liver function analyses, as well as for standard haematology. Similarly, at these times patients underwent 12 lead electrocardiography.

Assessment of side-effects

Each patient was asked the standard question 'Has your treatment agreed with you?' after blood pressure had been measured. If the answer was 'no', then they were asked to specify the type of effect, the severity, whether they felt it was related to the therapy and whether it had been so severe that they had felt it necessary to discontinue medication. All responses were recorded in patient record folders.

Compliance

All tablets were dispensed by the outpatient dispensary at Leicester Royal Infirmary. Patients were issued with a known excess of tablets than necessary at each visit and were requested to return the excess at the next visit. The number of tablets returned was recorded and a measure of compliance estimated.

24 h blood pressure control

On the day of an outpatient clinic visit, patients were asked not to take their morning dose of tablets. Each assessment took place in a morning clinic and patients were asked how many hours had elapsed since they had taken the previous day's therapy. In this way the control of blood pressure over a 24 h period could be assessed on once daily nitrendipine compared with 12 h post-dose measurements on twice daily nifedipine.

Statistical analysis

All information was recorded in confidential patient record folders and forwarded to a statistical adviser independent of Bayer UK for assessment. Statistical analysis was performed using Student's paired *t*-test comparing blood pressures at week 2 with those obtained at weeks 8 and 16. The possibility of a treatment order effect was investigated using the method of Hills & Armitage (1979). Results are expressed as mean $\pm$ s.e. mean.

Results

A total of 22 patients entered the study of whom 13 had received antihypertensive drug therapy before; the mean period of treatment before entry into the study was 2.3 months (range 1–7 months). Six patients were withdrawn due to intolerable side-effects of whom three had been previously treated. The remaining 16 patients who completed the experiment comprise the

basis upon which statistical analyses were performed. Thirteen patients were male, the mean age of the group was 48 ± 2.9 years, and the average blood pressures upon entry to the study were $170 \pm 5.5/95 \pm 3.0$ mm Hg supine and $170 \pm 4.8/108 \pm 1.4$ mm Hg standing. Eight patients smoked cigarettes and all subjects were caucasian.

Patients excluded from the analysis

Six patients did not complete the study, all of whom developed adverse side-effects to the active medication. Four subjects developed severe headaches; of these two patients were randomized to take first nitrendipine and two were on nifedipine first and developed their symptoms whilst taking the first doses of therapy. All four patients stopped their medication of their own accord and were withdrawn from the study when they were reviewed at week 5. One patient developed flushing, ankle swelling and headache on crossing over to nifedipine and was withdrawn at week 13. This subject had responded to low dose nitrendipine. One patient had developed severe ankle swelling on nitrendipine and was withdrawn at week 5.

Blood pressure

Blood pressure rose during the placebo phase of the study (Figure 2); supine diastolic pressure was significantly raised at week 2 compared with week 0 (100 ± 2.6 vs 95 ± 3.0 mm Hg, $P = 0.027$, Figure 2). Similarly standing diastolic pressure rose significantly (113 ± 2.4 vs 108 ± 1.4 mm Hg, $P = 0.036$, Figure 2). Between weeks 0 and 2 systolic blood pressures did not rise significantly in either position (Figure 2). Both agents lowered mean blood pressures although nitrendipine failed to reduce significantly standing diastolic pressure (Figure 2). In fact there were no significant differences in blood pressures obtained with either drug (Figure 2), although it can be seen that neither agent was totally successful as monotherapy in controlling blood pressure. Eleven patients failed to respond to low dose nitrendipine and 10 patients to low dose nifedipine. Of the 10 non-responders to nifedipine, seven patients were also non-responders to nitrendipine. The blood pressures in the non-responders failed to fall significantly when either agent was increased: on nifedipine, low dose to titrated dose, supine BP $161 \pm 5.4/91 \pm 2.9$ vs $158 \pm 4.2/92 \pm 3.3$ mm Hg (NS), standing BP $163 \pm 4.8/104 \pm 1.9$ vs $162 \pm 5.5/102 \pm 3.9$ mm Hg (NS) and on nitrendipine, low dose to titrated dose, supine BP $167 \pm 6.8/88 \pm 2.1$ vs $160 \pm$

Figure 2 Mean ($\pm$ s.e. mean) supine (open bars) and standing (hatched bars) blood pressures of 16 hypertensive patients during placebo, nitrendipine and nifedipine treatment. The study protocol was randomized and cross-over in design; therefore this is a diagrammatic plot of the results assuming nitrendipine was received first. * $P < 0.05$, ** $P < 0.01$, NS not significant.

$4.3/74 \pm 3.3$ mm Hg (NS), standing BP $170 \pm 7.6/108 \pm 1.7$ vs $159 \pm 7.7/106 \pm 3.2$ mm Hg (NS).

Using the methods of Hills & Armitage (1979) it was clear that there was a period effect. Therefore data were reanalysed after subgrouping results from individuals according to the therapy first received. It was then clear that the period effect was similar for both groups and not influenced by which treatment was first initiated. Assessment of the control of blood pressure over 24 h revealed that for patients taking nitrendipine this was less than optimal: eleven patients failed to respond to a dose of 20 mg in the morning and had to have it increased to 20 mg twice daily. This failure rate was similar to that observed on nifedipine but this drug is recommended to be administered twice daily.

Heart rate

At week 2 mean heart rate was 83 ± 3.7 beats min^{-1} supine and 91 ± 4.6 beats min^{-1} standing. Treatment with nifedipine for 6 weeks led to a significant fall in supine pulse rate (75 ± 3.1 beats min^{-1} , $P = 0.0012$) but no fall in standing pulse rate (87 ± 4.2 beats min^{-1} , NS). Nitrendipine did not significantly influence heart rate in either position (78 ± 4.6 supine, 92 ± 5.0 standing beats min^{-1} , NS). Analysing these data after dividing the results by which treatment was administered first revealed the same pattern, inferring this was not an order effect. There was no significant difference between heart rates after 6 weeks on either drug.

Weight, serum biochemistry and blood haematology

Weight did not change throughout the experiment. Similarly electrocardiographs, U+E, glucose, liver function tests and creatinine as well as standard haematology tests were all unaltered during the study.

Compliance

Compliance was assessed using tablet counts. During the placebo phase of the study, despite requiring to take six tablets a day, compliance was $94 \pm 1.2\%$. Whilst taking nifedipine, compliance was $95 \pm 1.1\%$; on nitrendipine this fell slightly to $89 \pm 2.9\%$ although this was not statistically significant. Subgrouping the data suggested that compliance rates were not affected by the order in which the treatments were received or by either drug being preferred.

Discussion

The results of this experiment demonstrate that nitrendipine is as effective as nifedipine in lowering blood pressure, although despite claims that nitrendipine is effective once daily (Hansson *et al.*, 1983), this study suggests that in a dose of 20 mg given orally daily blood pressure control was not satisfactory. In accord with a previous study, heart rate was not affected by chronic administration of nitrendipine (Hansson *et al.*, 1983), whereas pulse rates fell on nifedipine, achieving statistical significance in the supine position. Adverse events necessitating withdrawal were observed equally on each drug and neither influenced body weight, blood biochemistry or haematology. Compliance was excellent throughout the experiment, and did not appear to be influenced by the active medication taken at the time of assessment.

Therapy for essential hypertension using a stepped-care approach has been advocated for

some time (Moser *et al.*, 1977), although it has been realized that treatment with multiple agents increases non-compliance with a theoretical increase in side-effects (Gatley, 1968; Breckenridge, 1983). Thus there has been a desire to keep to a minimum the number of drugs and their frequency of administration. The calcium channel antagonist nifedipine in a slow release preparation provided a novel monotherapeutic agent (Gould *et al.*, 1983), although up to 25% of patients experience vasodilator side-effects and it has to be administered twice daily. Such problems may be reduced by the recent introduction of a lower strength 10 mg tablet for subsequent dose titration. Nitrendipine has been produced in an attempt to provide 24 h blood pressure control from once daily administration and to reduce unwanted side-effects. An early study suggested that 20 mg orally once daily was effective for 24 h and that increasing the dose to 40 mg once daily conferred no further benefit (Hansson *et al.*, 1983). However, this was not the case in our study and the withdrawal rate due to vasodilator side-effects was similar to that seen with nifedipine; however, in the present study the non-responders received nitrendipine 20 mg orally twice daily. In view of the possibility of order effects confounding the results, the data have been reanalysed to look for such events. However, no such errors were observed.

In summary therefore, nitrendipine appears to be a useful antihypertensive agent and lowered blood pressure in sixteen essential hypertensive patients. However it appeared to possess no advantages over the pre-existing dihydropyridine nifedipine when administered in a slow release formulation, and was less effective as a once daily medication.

We are grateful to Mr J. Bailey of Epsom, Surrey, for performing the statistical analyses and to Bayer (UK) Ltd for supplies of nitrendipine, nifedipine retard and matching placebo tablets for this experiment. We are indebted to Mrs Denise Jarvis for her expert secretarial assistance.

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(Received 28 July 1988,
accepted 14 November 1988)