A comparison of verapamil and nifedipine on quality of life

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1 Aspects of quality of life (symptoms, psychological well-being and activity) were evaluated by self-administered questionnaires in a 4 month randomised double-blind trial of titrated doses of verapamil slow release ($n = 41$) compared with nifedipine retard ($n = 40$). An untreated diastolic blood pressure of 95–115 mm Hg was required for inclusion in the trial.

2 The mean age in both groups was 55 years. A significant difference between the two drugs was found in the average reporting of symptoms with an increase on nifedipine ($P < 0.01$). The reporting of swollen ankles and flushing ($P < 0.05$) increased on nifedipine, and nocturia ($P < 0.05$) increased on verapamil. Measures of psychiatric morbidity tended to improve on verapamil and deteriorate on nifedipine. Only the change in cognitive function was significant between the drugs, being worse on nifedipine ($P = 0.05$).

3 There was no difference between the two groups in the fall in diastolic blood pressure (average 18 mm Hg on nifedipine and 17 mm Hg on verapamil). There was a significantly greater fall in systolic blood pressure on nifedipine (23 mm Hg) compared with verapamil (13 mm Hg) ($P < 0.01$).

4 The two drugs differed in their effects on measures of quality of life. The improvements in symptomatic complaints and psychological well-being on verapamil may have been due to inclusion in a trial, although we cannot exclude the possibility of a drug effect. Conversely the increase in symptoms and self-assessed cognitive impairment on nifedipine were considered to be side-effects of the drug.

Keywords calcium channel blockers nifedipine quality of life verapamil

Introduction

Mild to moderate essential hypertension is often a symptomless condition which is associated with an increased risk of cardiovascular events. Benefits of antihypertensive treatment have been established by various large placebo controlled trials showing a 40% reduction in stroke events in the actively treated group. Antihypertensive drugs however may produce side-effects which interfere with aspects of patients' everyday lives, leading to an impaired quality of life and possible non-compliance. Studies of established antihypertensive therapy have found that

adverse reactions may result in a high number of withdrawals, for example, 16% (MRC Working Party, 1981) and 32.7% (Curb *et al.*, 1985), in two studies over a 5 year period. Trials of antihypertensive therapy should, therefore, study all aspects of the effects of treatment.

This report presents data on two calcium channel blocking drugs that represent pharmacologically different groups. These drugs may be associated with different side-effects and may therefore have differing effects on quality of life.

Quality of life on calcium channel blockers has

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recently been studied and compared with that on β -adrenoceptor blocking drugs. Calcium channel blockers may have a favourable effect on quality of life when compared with β -adrenoceptor blockers (Fletcher *et al.*, 1989).

The present study compared the effect on quality of life of nifedipine and verapamil in a double-blind trial of patients with mild to moderate essential hypertension.

Methods

Trial participants aged between 30 and 70 years were recruited from a general practice in North Surrey. The subjects were either newly diagnosed out-patients, or treated hypertensives who failed to respond satisfactorily to previous therapy. Previously treated hypertensive patients had to satisfy entry criteria during a 3 week wash-out period. Blood pressure entry criteria were a sitting, untreated diastolic blood pressure (DBP) of 95–115 mm Hg (phase V) on two consecutive occasions within 3 weeks, and a difference between the readings of 10 mm Hg or less. Patients with abnormal haematological or biochemical screen results were excluded, as were patients with the usual contra-indications for the two drugs. Patients were also excluded if they were known to be intolerant to calcium channel blockers, were insulin requiring diabetics, if they were receiving digoxin, antidepressants or major tranquillisers, or when informed consent was refused.

The study was approved by the ethics committee of the United Medical and Dental Schools of Guy's and St Thomas' Hospitals.

Blood pressure was measured at morning clinics with a Hawksley random zero sphygmomanometer. Diastolic blood pressure was recorded as Korotkoff Phase V. Blood pressure was taken while patients sat with their arms supported at heart level and on each occasion two readings were made after a 5 min rest period and with a 5 min interval between measurements. The mean of the two readings was used to evaluate blood pressure.

The trial had two stages: a single blind placebo-only period of 3 weeks (following a 3 week no-treatment period) and a 4 month double-blind trial. The patients were randomised to 240 mg verapamil slow release (SR) once daily (+ placebo nifedipine) plus placebos in the evening, or 20 mg nifedipine retard twice daily (+ placebo verapamil). Blood pressure was assessed at 2, 4, 6, 12 and 16 weeks. If the response to treatment was not satisfactory (DBP > 90 mm Hg) the doses were increased (in two divided doses daily)

to 360 mg and 480 mg verapamil, as required, or 60 mg and 80 mg nifedipine. Returned tablets were counted at each visit as a measure of compliance.

Quality of life was assessed through self-administered questionnaires completed at the end of the run-in placebo period, and at the end of the double-blind trial period. Quality of life in patients who withdrew from the trial was assessed at the time of withdrawal.

Symptomatic side-effects of treatment were evaluated from a questionnaire which included 30 symptoms and side-effects. A complaint rate (the proportion of reported complaints) was derived from this checklist. All questions have been shown to be valid, repeatable and sensitive to the effects of antihypertensive therapy (Bulpitt *et al.*, 1974; Bulpitt & Dollery, 1973). The net change in the reporting of symptoms (% gaining a symptom – % losing a symptom) was calculated. An activity and perceived well-being measure was based on the health status index of Fanshel & Bush (1970) which provides a score ranging from 0 at death to 100 at perfect health. This was derived from responses in the questionnaire on work, absence due to sickness and interference with lifestyle caused by treatment. Psychiatric morbidity was assessed by the Symptom Rating Test (Kellner & Sheffield, 1973), both overall and for five sub-scales: anxiety, depression, somatic, cognitive and hostility. This test has been validated in psychiatric patients and shown to be sensitive to the effects of psychotropic drugs. The methods have been described in connection with other trials (Bulpitt & Fletcher, 1985).

The questionnaires were completed at the surgery prior to blood pressure measurement and sent to the Epidemiology Research Unit for quality control and analysis. The data were analysed using a SAS statistical package (SAS, 1985). All data processing and analyses were done blind to the treatment code.

Statistical methods

Sample size calculations showed that 40 patients in each group were needed to detect a 5.3 difference in the complaint rate at the 5% level of significance and 90% power. This order of difference has previously been reported in a comparison of verapamil and propranolol (Fletcher *et al.*, 1989).

Blood pressure data were examined by analysis of variance. The Wilcoxon rank sum test was used to compare quality of life scores at randomisation and after treatment. Confidence intervals on the changes in scores were computed using

standard parametric methods. Fisher's exact probability test and McNemar's test were used to test between and within drug differences, respectively, for the reporting of individual symptoms and side-effects.

Results

Withdrawals

Of the 83 patients who entered the trial, two withdrew during the placebo period; the reasons were blood pressure below 95 mm Hg (1) and variable blood pressure (1). Of the remaining 81 patients who started active treatment, 10 withdrew (4 on verapamil) before the end of the double-blind period. The reasons for withdrawal were abnormal ECG, headache, depression and disorientation for the four patients on verapamil. Reasons for withdrawal on nifedipine were headache (2) loss of libido (2) inability to sleep (1) and flushing (1).

Blood pressure

Blood pressure at randomisation is given in Table 1. Baseline systolic pressure averaged 4 mm Hg higher on nifedipine than verapamil ($P > 0.2$).

For both drugs there were significant ($P < 0.001$) falls in both systolic and diastolic blood pressure at each visit when compared with baseline pressure.

At each visit the fall in systolic blood pressure was significantly greater ($P < 0.05$ and $P < 0.01$) on nifedipine compared with verapamil (Table 2). There were no significant between drug differences in change in diastolic blood pressure.

In those patients that completed the trial, 92% (verapamil) and 91% (nifedipine) were considered to have had a satisfactory blood pressure response (defined as a diastolic blood pressure

Table 1 Background characteristics (mean (s.d.)) of patients randomised to active treatment

	Verapamil (n = 41)	Nifedipine (n = 40)
Mean age (years)	55.1 (7.8)	54.8 (9.1)
Systolic blood pressure (mm Hg)	152.9 (13.6)	157.0 (15.1)
Diastolic blood pressure (mm Hg)	100.1 (5.0)	101.9 (5.7)
% male	53.7	50.0
% employed	63.4	57.5
% housework	14.6	20.0
% retired	14.6	20.0
Complaint rate	19.9 (10.1)	19.5 (10.9)
Health status index	94.1 (6.6)	93.5 (7.0)
Psychiatric morbidity		
Total	11.4 (12.4)	12.1 (9.4)
Anxiety	2.4 (2.9)	3.1 (3.1)
Depression	2.1 (2.4)	2.1 (2.0)
Somatic	2.3 (2.5)	2.3 (2.1)
Cognitive	2.5 (3.6)	1.9 (2.8)
Anger-hostility	2.2 (2.7)	2.5 (2.8)

≤ 90 mm Hg). Nine patients (four on verapamil) were on the maximum dose at the end of the 4 month period. Compliance was good, averaging 98% on verapamil and 99.7% on nifedipine.

Quality of life

The background characteristics of the patients randomised to the two treatment groups were similar (Table 1). There were no significant differences between the two groups in the quality of life scores at commencement of active treatment.

The within group change in measures from baseline to the end of the trial are shown in Table 3, together with the 95% confidence interval for

Table 2 Mean (s.d.) blood pressure changes compared with baseline in patients completing the double-blind phase

	Week 2	Week 6	Week 16
<i>Verapamil SR</i> (n = 37)			
SBP (mm Hg)	-9.4 (10.4)	-12.3 (9.9)	-13.1 (14.8)
DBP (mm Hg)	-13.5 (6.7)	-14.2 (5.9)	-16.6 (6.7)
<i>Nifedipine retard</i> (n = 34)			
SBP (mm Hg)	-16.7 (12.9)*	-23.3 (13.3)**	-22.5 (13.3)**
DBP (mm Hg)	-14.4 (9.2)	-17.7 (6.9)	-18.0 (8.1)

Between drug differences: * $P < 0.05$, ** $P < 0.01$.

Table 3 Change in absolute values for quality of life variables from baseline to end of trial. Figures are mean with (95% confidence interval)

		Verapamil		Nifedipine	95% confidence interval for between drug differences (verapamil–nifedipine)
	<i>n</i>		<i>n</i>		
Complaint rate (%)	30	-1.90 (-4.06, 0.26)	35	3.67 (0.79, 6.55)	(-9.19, -1.94)**
Health status index	41	-0.79 (-3.71, 2.12)	40	-0.75 (-2.78, 1.28)	(-3.58, 3.49)†
Psychiatric morbidity					
Total	34	-1.50 (-4.51, 1.52)	36	1.71 (-0.28, 3.71)	(-6.72, 0.30)
Anxiety	34	-0.11 (-0.81, 0.58)	36	0.35 (-0.41, 1.11)	(-1.48, 0.55)
Depression	34	-0.26 (-0.93, 0.40)	36	0.04 (-0.44, 0.53)	(-1.11, 0.49)
Somatic	33	-0.33 (-1.04, 0.38)	36	0.25 (-0.16, 0.65)	(-1.36, 0.21)
Cognitive	34	-0.56 (-1.44, 0.32)	36	0.58 (-0.17, 1.33)	(-2.28, -0.01)*
Hostility	37	-0.22 (-1.00, 0.56)	37	0.48 (-0.56, 1.52)	(-1.98, 0.58)

Between drug comparison: * $P = 0.05$, ** $P < 0.01$.

†Negative values for health status index imply deterioration. Negative values for all other scores imply improvement.

between drug differences and level of statistical significance for these differences for $P \leq 0.05$ and greater. A significant difference between the two treatments was found for the complaint rate ($P < 0.01$) and for cognitive function ($P = 0.05$) (Table 3). For individual symptoms there were no significant differences between the two treatments (Table 4). Over the period of active treatment more patients on nifedipine reported swollen ankles ($0.02 < P < 0.05$) and flushing ($0.02 < P < 0.05$) than subjects on verapamil;

while more patients on verapamil reported nocturia ($0.02 < P < 0.05$) (Table 4). The excess of headaches on nifedipine was not significant ($P = 0.3$).

Discussion

Ten patients (four on verapamil) withdrew because of side-effects. This withdrawal rate is comparable with other studies (MRC Working Party, 1981; Fletcher *et al.*, 1989). At the end of the trial, patients treated with nifedipine had more complaints than patients on verapamil. In the verapamil group, constipation and nocturia were the most commonly reported symptoms arising during the trial, while symptoms commonly reported on nifedipine included swollen ankles, flushing and headaches. Constipation has been found to be a frequent side-effect of verapamil (Fenech & Pickup, 1984; Fletcher *et al.*, 1989). Other reported reactions include flushing, dizziness and nausea (Consumers Association, 1984; Lewis *et al.*, 1978; Midtbo *et al.*, 1982). Case reports of disturbing dreams with long-acting verapamil have recently been reported in three people who were treated for migraine (Kumar & Hodges, 1988), but not previously described on nifedipine. The present study showed a non-significant 10% increase in the reporting of vivid dreams or nightmares on both drugs. Adverse effects on nifedipine include headaches, flushing, dizziness, peripheral oedema and weakness (American Hospital Formulary, 1986; Nifedipine-Atenolol Study Review Committee, 1988; Terry, 1982). An increase of eye pain, but not blurred vision, has

Table 4 Change in the reporting of symptoms and side-effects within treatment (% gain – % loss) for verapamil and nifedipine for between drug differences greater than 5%

Symptom	<i>n</i>	Verapamil	<i>n</i>	Nifedipine
Sleepiness	37	-2.7%	37	+5.4%
Weakness	37	0.0%	38	+15.8%
Swollen ankles	37	-2.7%	38	+18.4%
Diarrhoea	38	-7.9%	38	+7.9%
Constipation	36	+13.9%	39	+2.6%
Dry mouth	36	0.0%	39	+15.4%
Runny nose	36	-8.3%	38	-2.6%
Flushing	35	+5.7%	39	+23.1%
Nausea	40	0.0%	39	-15.4%
Itch	40	-2.5%	38	+5.3%
Headaches	39	-12.8%	39	+10.3%
Walking pace	38	-7.9%	39	+5.1%
Nocturia	41	+19.5%	40	+7.5%
Cramps	36	-8.3%	38	+5.3%
Shaking hands	36	-2.8%	38	+7.9%
Stomach pain	35	+5.7%	35	0.0%
Heartburn	34	-8.8%	38	-2.6%

No significant between treatment differences ($P < 0.05$).

been reported in a comparison of nifedipine with captopril (Coulter, 1988). No increase in the reporting of blurred vision on either treatment was found in the present study. There was also no increase in the reporting of dizziness or nausea in patients on either drug. As this was a small trial infrequent side-effects were not likely to be detected and it is unlikely that there was sufficient power to detect subtle changes.

In a study comparing the effects of a single-dose administration of nifedipine (10 mg) or verapamil (160 mg) over a 6 h period, nifedipine significantly increased renal excretion of water and sodium (Leonetti *et al.*, 1982). There was only a modest increase with verapamil. The present study, of prolonged drug administration, showed that while both groups reported an increase in nocturia, this was only significant for the verapamil group ($P < 0.05$).

There was a 31% deterioration in the cognitive score on nifedipine, compared with a 22% improvement on verapamil ($P = 0.05$). The increase on verapamil may reflect either the higher score at baseline and regression to the mean, or an improvement in cognitive function due to some pharmacological effect, or participation in the trial. This trial effect has been described in other studies (Fletcher *et al.*, 1988, 1989; Mann, 1985). Analysis of the change in scores classified by baseline score showed that regression to the mean did not account for these changes. We have found a similar deterioration in self-reported cognitive function on nifedipine: in a recent trial comparing pinacidil with nifedipine there was a 9% deterioration in the cognitive score in the nifedipine group and a 17% improvement on pinacidil ($P < 0.05$) (Fletcher & Bulpitt, 1989).

In a single-blind, cross-over comparison of long acting nifedipine with enalapril in 10 elderly hypertensives there were two cases of 'moderate clouding of mentation' on nifedipine (Gilchrist *et al.*, 1988).

Seven items comprise the cognitive score describing problems with concentration and memory (5 and 2 questions, respectively). Increased reports of problems in the nifedipine group were not restricted to any particular item.

It is possible that the observed self-reported cognitive function differences between the drugs at the end of the trial may have been due to an improvement with verapamil rather than a deterioration with nifedipine. This explanation would appear less likely since there is no evidence of this effect of verapamil in the literature. A further possibility is that the greater fall in systolic pressure on nifedipine was responsible for the changes in cognitive function. However, the effect remained after adjustment for the size

of fall in pressure. Farmer *et al.* (1987) also failed to find a relationship between objective test of cognitive function and blood pressure in a population study. The present data suggest that nifedipine may be associated with self-reported cognitive impairment; this suggestion should be further investigated using objective assessments.

Between drug comparison revealed no significant difference in the health status index and in the anxiety, depression, somatic and hostility scores over the period of active treatment. Although there was a significant increase in the complaint rate on nifedipine, there was no marked change in the health status index score. This may suggest that the adverse reactions were not severe enough to affect general well-being. The present study suggests that verapamil has certain advantages over nifedipine in quality of life measures. Verapamil also produced less adverse effects in a trial vs propranolol (Fletcher *et al.*, 1989). Verapamil patients showed an improvement in psychiatric morbidity scores, and reported fewer symptoms when compared with those who received propranolol.

The complaint rate significantly worsened on nifedipine and patients randomised to nifedipine showed a general deterioration in psychological well-being whilst on active treatment compared with a general improvement found in the verapamil group.

Both drugs have been shown to have a significant hypotensive effect in patients treated for mild to moderate hypertension (Lewis *et al.*, 1978; Midtbo *et al.*, 1982; Nifedipine-Atenolol Study Review Committee, 1988). The significant falls in both systolic and diastolic pressure found in the present study confirm these findings. The greater fall in systolic pressure for patients treated with nifedipine ($P < 0.01$) may reflect the higher baseline systolic blood pressure in this group, or a true difference between the drugs. It has been previously suggested that, in comparison with many other antihypertensive drugs, verapamil lowers systolic pressure less than would be expected from its effect on diastolic pressure (Bulpitt, 1986). As goal blood pressure was based on measurement of diastolic pressure it is not surprising that in the present trial reduction in diastolic pressure was similar for the two drugs but the reduction in systolic pressure differed between the groups.

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