Lisinopril and nifedipine: No acute interaction in normotensives

K. R. LEES & J. L. REID

University Department of Materia Medica, Stobhill General Hospital, Glasgow G21 3UW

1 A double-blind, four period crossover study was undertaken to test for an interaction between single oral doses of nifedipine retard (20 mg) and lisinopril (20 mg) in normal subjects.

2 Side effects with both drugs were mild and the incidence was additive.

3 Blood pressure (BP) was lowered by nifedipine for 4 h, by lisinopril for 48 h and the combination showed simply additive effects. Standing heart rate was higher after the combination than after single treatment.

4 Plasma angiotensin converting enzyme (ACE) and renin activity (PRA), aldosterone, noradrenaline and adrenaline levels showed no evidence of an interaction.

5 The pharmacokinetics of lisinopril were unaltered by nifedipine and *vice versa*.

6 There is no evidence of a pharmacokinetic or pharmacodynamic interaction between single oral doses of nifedipine and lisinopril.

Keywords lisinopril nifedipine pharmacodynamics pharmacokinetics drug interaction

Introduction

Angiotensin converting enzyme inhibitors (ACEI) and calcium antagonists are two groups of drugs which are increasingly used for the treatment of hypertension. We have observed excellent therapeutic responses in a few individual patients to the combination of ACEI and calcium antagonists. We wished to assess the effects of single doses of combined therapy in a group of normal subjects because:

(a) Both calcium antagonists and ACEI can cause marked, acute falls in blood pressure. In the case of nifedipine the fall is closely related to drug plasma levels (Pasanisi & Reid, 1983) and compensated for, at least in part, by reflex sympathetic activation. With ACEI the acute fall in blood pressure is particularly dependent on sodium status and is not usually associated with reflex sympathetic activation (Hodsman *et al.*, 1983).

(b) Vasodilators, including endralazine, verapamil and dihydropyridine calcium antagonists, increase liver blood flow acutely

Meredith *et al.*, 1985) and may profoundly alter the disposition and metabolism of other drugs like prazosin (Pasanisi *et al.*, 1984) or even their own metabolism (Meredith *et al.*, 1983, 1985).

The aim of this study was to examine in detail the pharmacokinetics and pharmacodynamics of the combination of lisinopril and nifedipine.

Methods

Subjects

Twelve male volunteers were recruited after screening by history, physical examination, urinalysis, electrocardiograph and routine laboratory tests of haematology and serum biochemistry to ensure good health. Written informed consent was obtained from all subjects and the study design was approved by the local ethics review committee. The age of the volunteers was 26 ± 5 years (mean $\pm$ s.d.), their

Correspondence: Dr K. R. Lees, Department of Materia Medica, Stobhill General Hospital, Glasgow G21 3UW

weight was 69 ± 9 kg and their height was 174 ± 6 cm.

Design

This was a double-blind, four period, crossover study using a Latin square design balanced for carry over effects in 12 subjects. The four treatments, each given as a single oral dose at least seven days apart, were as follows:

1. Lisinopril 20 mg + placebo nifedipine.
2. Nifedipine 20 mg (Adalat Retard, Bayer UK Ltd) plus placebo lisinopril.
3. Nifedipine retard 20 mg plus lisinopril 20 mg.
4. Placebo nifedipine plus placebo lisinopril.

At the beginning of each study period, subjects attended the Clinical Pharmacology Research Unit at 08.30 h, having fasted from 22.00 h on the previous night apart from a light liquid breakfast of 100 ml of orange juice. Each subject was asked to empty his bladder and then an antecubital venous cannula (Venflon®) was inserted and flushed with heparinised saline. After at least 20 min rest in the supine position, the predosing recordings were taken and then the appropriate tablets were given with 200 ml of water. Each recording followed the same sequence: blood pressure and heart rate were recorded by Sentron semiautomatic sphygmomanometer (Bard Biomedical) in duplicate after at least 10 min supine rest, a venous blood sample was drawn and then blood pressure and heart rate were recorded after 2 and 5 min standing. The sample times were 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 24, 48, 72 and 96 h from dosing. In addition, samples for plasma catecholamines were collected before dosing and after 1, 2 and 4 h. Samples for plasma ACE activity were collected before dosing and after 2, 4, 6, 10, 24 and 48 h. Plasma renin activity and aldosterone were measured at 0, 2, 4, 6, 10, 24 and 48 h.

All urine voided from time of dosing until 96 h postdosing was collected and aliquots were stored, with a record of the total volume, representing the following times after dosing: 0–2, 2–4, 4–6, 6–10, 10–24, 24–48, 48–72, and 72–96 h.

The subjects were questioned about symptoms at each of the recording times and any positive replies were noted.

Laboratory methods

i. *Nifedipine* All samples for drug assays were protected from light and were centrifuged and separated under sodium light. Plasma levels of

nifedipine were assayed by high pressure liquid chromatography (Waller *et al.*, 1984). The intra and inter assay coefficients of variation ranged from 3.8 to 5.4% and 4.2 to 7.2% respectively. The limit of detection was 0.5 ng ml^{-1} .

ii. *Lisinopril* Lisinopril was measured by radio-immunoassay of plasma samples (Hichens *et al.*, 1981). The inter assay coefficient of variation ranged from 15–24%. The limit of detection was 2.1 ng ml^{-1} . Urine samples were assayed after appropriate dilution in buffer.

iii. *Plasma angiotensin converting enzyme activity* Plasma ACE activity was measured by the h.p.l.c. assisted assay of Chiknas (1979), for which the inter and intra assay coefficients of variation were 6.1% and 2.3% respectively and the limit of detection was 0.5 EU/l.

iv. *Catecholamines* Plasma noradrenaline and adrenaline were measured by the catechol-*o*-methyltransferase radioenzymatic method of da Prada & Zurcher (1976). For noradrenaline the inter and intra assay coefficients of variation were 15% and 13% respectively while for adrenaline these were 20% and 15%.

v. *Aldosterone* Plasma aldosterone levels were measured by a direct radioimmunoassay (McKenzie & Clements, 1974). The inter and intra assay coefficients of variation were 11.0% and 7.3% respectively.

vi. *Renin activity* An indirect radioimmunoassay was used which measures the rate of production of angiotensin I in a standard incubation mixture (Derckx *et al.*, 1979). The inter and intra assay coefficients of variation were 7.0% and 5.5% respectively.

Routine laboratory analysis

Urinalysis was carried out on freshly voided morning specimens by dipstix (Multistix-Ames Laboratories). The haematology measurements were by Coulter Counter and the biochemical analyses were performed on a SMA-C auto-analyser using standard methods.

Data analysis

i. *Pharmacokinetic analysis* Standard methods were used to select an appropriate pharmacokinetic model for each drug (Gibaldi & Perrier, 1982). Least squares nonlinear regression analysis was used to fit the data to the models and the parameter estimates obtained for each drug when given alone were compared with those for the drugs given in combination. These comparisons were made by Student's paired *t*-test (two-tailed) taking 0.05 as the critical level of significance.

The cumulative urinary excretion of lisinopril was calculated in the presence and absence of nifedipine and these values were also compared by Student's *t*-test.

ii. *Statistical methods* An effect of treatment order was excluded by repeated measures analysis of variance. Plasma hormones were analysed by repeated measures analysis of covariance, following logarithmic transformation, taking the pretreatment value as covariate. Plasma angiotensin converting enzyme activity was converted to percentage ACE inhibition before analysis: %ACE inhibition = 100 (1-ACE/pretreatment ACE). To test specifically for an effect of nifedipine on the inhibition produced by lisinopril, analysis of variance on these two treatment periods alone was performed.

Repeated measures analysis of variance was used to compare the effect of the treatments on blood pressure and heart rate. Main effects and treatment interactions were tested. Where appropriate multiple pairwise comparisons of the individual treatment means were made for each time using the Tukey method for calculating confidence intervals (Winer, 1971). All of the analyses of variance were carried out on an ICL 2988 computer using the programme BMDP2V.

The study had 80% power of detecting the following changes for lisinopril and nifedipine pharmacokinetics respectively: 30% and 25% difference in AUC; 40% and 25% difference in half-life.

Results

Symptoms

These are summarised in Table 1. Nifedipine retard appeared to cause headache in three or four of the 12 subjects and lisinopril caused lightheadedness in two subjects, each regardless of whether the drugs were given singly or in combination. None of these symptoms was severe and there was otherwise no serious adverse effect nor change in the laboratory screening tests.

Blood pressure and heart rate

(a) *Supine* Analysis of variance revealed treatment-time interactions for nifedipine (N) and lisinopril (L) separately (N $P < 0.02$, L $P < 0.001$ systolic; N $P < 0.0001$, L $P = 0.06$ diastolic; N $P < 0.01$, L $P = 0.18$ heart rate) but no interaction between the two drugs ($P = 0.17$ systolic; $P = 0.31$ diastolic; $P = 0.99$ heart rate). Their effects can therefore be described as not significantly different from additive.

(b) *Standing* Standing blood pressure showed greater variation than supine but a trend towards the same results was evident: N $P = 0.06$, L $P < 0.0001$, NL $P = 0.60$ systolic; N $P = 0.13$, L $P < 0.01$, NL $P = 0.92$ diastolic; N $P < 0.0001$, L $P = 0.59$, NL = 0.43 heart rate.

For clarity, Figure 1 shows only placebo subtracted data; absolute values for 0, 2, 4, 8 and 24 h after dosing are shown in Table 2.

Plasma hormones

Lisinopril produced profound inhibition of plasma ACE with increased renin activity and reduced aldosterone, but nifedipine retard did not alter these responses ($P = 0.46$, $P = 0.83$, $P = 0.91$ respectively) (Table 3). No treatment caused any alteration in plasma catecholamine levels ($P = 0.18$ noradrenaline, $P = 0.98$ adrenaline).

Lisinopril pharmacokinetics

The 24 data sets (12 subjects with two treatment periods each) were all adequately described by a one-compartment model. For the majority of data sets, zero order absorption allowed better modelling of the drug levels. Thus, the model which was used gave estimates of clearance/bioavailability, volume of distribution/bioavailability, $t_{\max}$ and t_{lag} . Estimates of these parameters for lisinopril alone and for lisinopril plus nifedipine respectively were as follows: clearance 13.5 ± 6.4 and $15.8 \pm 5.7 \text{ l h}^{-1}$, $P = 0.35$; volume of distribution 87 ± 30 and $110 \pm 85 \text{ l}$, $P = 0.36$; $t_{\max}$ 6.2 ± 1.5 and $6.8 \pm 1.3 \text{ h}$, $P = 0.27$; t_{lag} $1.1 \pm$

Table 1 Summary of symptoms

	Nifedipine + placebo	Lisinopril + placebo	Nifedipine + lisinopril	Placebo + placebo
Headache	4	1	5	1
Lightheadedness	1	3	3	1
Other	Sore throat	—	Diarrhoea	Tired

Figure 1 Supine diastolic blood pressure and erect heart rate, placebo corrected, after nifedipine (▲), lisinopril (◆) and nifedipine + lisinopril (■), $n = 12$. Changes were significant by analysis of variance.
* $P < 0.05$ compared with placebo, Tukey method.

Table 2 Supine and standing BP (mm Hg) and HR (beats min⁻¹) (mean $\pm$ s.d. $n = 12$) following placebo (P), nifedipine retard 20 mg (N), lisinopril 20 mg (L) and nifedipine + lisinopril (NL) at selected times after dosing. Statistical analysis is presented in the text, * represents difference from placebo at $P < 0.05$ for single time point (Tukey comparison).

		Time (h)					
Supine		0	2	4	8	24	
Systolic BP	P	117 $\pm$ 12	114 $\pm$ 9	117 $\pm$ 5	118 $\pm$ 9	123 $\pm$ 7	
	NL	120 $\pm$ 14	112 $\pm$ 8	104 $\pm$ 11*	112 $\pm$ 9*	120 $\pm$ 11	
	N	123 $\pm$ 7	114 $\pm$ 8	114 $\pm$ 9*	119 $\pm$ 8	124 $\pm$ 11	
	L	123 $\pm$ 10	115 $\pm$ 8	111 $\pm$ 9*	111 $\pm$ 7*	120 $\pm$ 10	
Diastolic BP	P	65 $\pm$ 6	64 $\pm$ 9	64 $\pm$ 8	55 $\pm$ 6	66 $\pm$ 7	
	NL	64 $\pm$ 6	56 $\pm$ 5*	53 $\pm$ 8*	50 $\pm$ 8	57 $\pm$ 11	
	N	67 $\pm$ 6	59 $\pm$ 10*	61 $\pm$ 8	59 $\pm$ 11	62 $\pm$ 12	
	L	65 $\pm$ 6	62 $\pm$ 6	57 $\pm$ 7*	52 $\pm$ 8	59 $\pm$ 7	
Heart rate	P	61 $\pm$ 12	56 $\pm$ 11	54 $\pm$ 11	63 $\pm$ 12	66 $\pm$ 11	
	NL	60 $\pm$ 13	63 $\pm$ 13	61 $\pm$ 10*	66 $\pm$ 14	69 $\pm$ 14	
	N	62 $\pm$ 12	63 $\pm$ 13	57 $\pm$ 10	62 $\pm$ 10	67 $\pm$ 13	
	L	60 $\pm$ 10	57 $\pm$ 9	60 $\pm$ 8*	62 $\pm$ 9	67 $\pm$ 12	
Erect							
Systolic BP	P	120 $\pm$ 8	119 $\pm$ 10	118 $\pm$ 10	119 $\pm$ 13	125 $\pm$ 14	
	NL	124 $\pm$ 7	119 $\pm$ 14	113 $\pm$ 7	107 $\pm$ 11*	121 $\pm$ 13	
	N	127 $\pm$ 9	121 $\pm$ 4	121 $\pm$ 14	117 $\pm$ 10	123 $\pm$ 11	
	L	124 $\pm$ 10	122 $\pm$ 8	107 $\pm$ 10*	108 $\pm$ 13*	121 $\pm$ 12	
Diastolic BP	P	72 $\pm$ 9	73 $\pm$ 8	72 $\pm$ 11	67 $\pm$ 11	75 $\pm$ 9	
	NL	73 $\pm$ 9	67 $\pm$ 9	67 $\pm$ 7	60 $\pm$ 9	64 $\pm$ 7	
	N	78 $\pm$ 5	70 $\pm$ 8	73 $\pm$ 11	69 $\pm$ 8	73 $\pm$ 11	
	L	75 $\pm$ 8	69 $\pm$ 8	69 $\pm$ 7	55 $\pm$ 10*	68 $\pm$ 8	
Heart rate	P	73 $\pm$ 15	67 $\pm$ 15	73 $\pm$ 18	86 $\pm$ 17	82 $\pm$ 11	
	NL	74 $\pm$ 15	81 $\pm$ 18*	81 $\pm$ 16	90 $\pm$ 17	88 $\pm$ 16	
	N	72 $\pm$ 14	76 $\pm$ 14	80 $\pm$ 13	81 $\pm$ 13	83 $\pm$ 11	
	L	79 $\pm$ 11	71 $\pm$ 12	75 $\pm$ 13	85 $\pm$ 11	86 $\pm$ 13	

Table 3 Median with 95% confidence limits for plasma renin and aldosterone following lisinopril 20 mg orally. Normal ranges are 4–12 ngAI ml⁻¹ h⁻¹ for renin and 12–125 pg ml⁻¹ for aldosterone. Nifedipine did not alter the response to lisinopril ($P = 0.83$ and $P = 0.91$ respectively).

		Renin (ngAI ml ⁻¹ h ⁻¹)			Aldosterone (ng ml ⁻¹)		
	Time (h)	Median	95% limits		Median	95% limits	
Lisinopril	0	7.2	4.4	11.5	105	80	139
	2	18.3	10.2	32.9	76	58	99
	4	38.2	20.2	72.1	58	40	84
	6	78.1	34.0	179.1	50	30	84
	10	57.5	26.7	123.7	52	32	86
	24	55.0	33.8	89.5	89	72	109
	48	41.5	29.3	57.5	122	105	141
Nifedipine/ lisinopril	0	8.2	4.9	13.7	108	80	147
	2	29.3	15.0	57.2	57	42	78
	4	37.8	16.3	87.4	54	42	68
	6	79.9	44.3	144.1	53	36	79
	10	57.5	29.9	110.6	82	63	107
	24	48.8	25.7	92.8	71	54	95
	48	35.4	21.5	58.2	120	102	141

Figure 2 Urinary recovery of lisinopril, in mg per collection period, following a single oral dose of lisinopril 20 mg in presence (▨) and absence (■) of nifedipine retard 20 mg orally.

0.6 and 0.8 ± 0.5 h, $P = 0.12$. Thus, the paired estimates of area under the curve were 1715 ± 612 and 1438 ± 536 ng ml⁻¹ h; their half-lives were 5.5 ± 3.0 and 4.9 ± 2.2 h; and estimated maximum concentrations were 144 ± 25 and 132 ± 42 ng ml⁻¹ respectively.

Urine analyses

The total urinary recovery of lisinopril after 96 h was 10.3 ± 3.3 mg after lisinopril alone and 10.0 ± 3.9 mg after the combination of drugs, $P = 0.8$. These figures represent 51.5% and 49.9% recovery of the administered dose. The profile of excretion is displayed in Figure 2.

The creatinine clearance and urinary sodium excretion measured over the 24 h following each treatment were 99 ± 19 ml min⁻¹ and 199 ± 44 mmol respectively. Neither was altered by treatment ($P = 0.85$, $P = 0.19$).

Nifedipine retard pharmacokinetics

The 24 data sets were all adequately described by a one compartment model. In this case, for the majority of data sets, first order absorption allowed better modelling of the drug levels. Thus, the model which was used gave estimates of four parameters namely A , k_e , k_a and t_{lag} . Estimates of these parameters for nifedipine alone and for nifedipine plus lisinopril respectively were as follows: A 67 ± 25 and 73 ± 52 ng ml⁻¹, $P = 0.63$; k_e 0.22 ± 0.06 and 0.23 ± 0.05

h⁻¹, $P = 0.36$; k_a 5.4 ± 7.8 and 3.4 ± 3.9 h⁻¹, $P = 0.5$; t_{lag} 0.33 ± 0.21 and 0.25 ± 2.4 h, $P = 0.44$. Thus, the paired estimates of area under the curve were 267 ± 82 and 255 ± 125 ng ml⁻¹ h; the half-lives for k_e were 3.4 ± 0.9 and 3.2 ± 0.8 h; the estimated maximum concentrations were 44.1 ± 19.5 and 41.8 ± 20.7 ng ml⁻¹; and times of peak concentrations were 1.7 ± 1.1 and 1.6 ± 0.7 h.

Discussion

Following treatment with nifedipine retard and lisinopril the symptoms which were elicited were mild and predictable: headache with nifedipine and mild lightheadedness with lisinopril. When given in combination the incidence of these symptoms did not appear to be altered although fewer subjects were then asymptomatic.

Both nifedipine and lisinopril lowered blood pressure when administered individually. Nifedipine retard had an earlier onset of action and shorter duration than lisinopril. Its effect was less profound but it appears that a compensatory tachycardia occurred which attenuated the response. No significant interaction between the treatments was detected, i.e. the effects were simply additive. Despite the compensatory tachycardia which was noted with nifedipine, no effect of any treatment on plasma catecholamines was detected.

Lisinopril had profound effects on plasma

ACE activity, renin activity and aldosterone levels, but nifedipine did not alter these responses.

The pharmacokinetics of nifedipine were not altered by the addition of lisinopril, nor were the pharmacokinetics of lisinopril altered by the addition of nifedipine. The wide assay variation was countered by the number of samples collected and the crossover design of the study. The study had 80% power of detecting a 30% change in AUC. Smaller changes in the pharmacokinetics would not be likely to have clinical significance. The urinary recovery of lisinopril shows that the bioavailability of lisinopril in these subjects was approximately 50%.

In conclusion, this study has demonstrated

that the effects of nifedipine retard and lisinopril on blood pressure are additive, but lisinopril does not appear to attenuate the compensatory tachycardia which is sometimes seen with nifedipine, and that the profile of side effects seen with the combination is simply the sum of those seen when the drugs are given singly. No evidence of a pharmacokinetic interaction between the drugs was detected. Thus the combination of nifedipine retard and lisinopril appears to be free from any pharmacokinetic or pharmacodynamic interaction.

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