An assessment of lacidipine and atenolol in mild to moderate hypertension

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- 1 The aim of this randomised, double-blind four way crossover study was to assess the interaction between the new calcium antagonist, lacidipine and atenolol, in patients with mild to moderate hypertension.
- 2 Sitting blood pressure at 4 h post-dosing with lacidipine (4 mg) and atenolol (100 mg) alone was significantly lower compared with placebo ($137/89 \pm 3/3$ mm Hg; $142/89 \pm 5/3$ mm Hg; and $154/98 \pm 5/3$ mm Hg respectively; $P < 0.001$). Co-administration of both drugs produced a significant additive effect compared with atenolol and lacidipine alone ($124/80 \pm 4/2$ mm Hg; $P < 0.002$).
- 3 Heart rate on treatment with lacidipine alone was significantly greater at 4 h compared with placebo (86 ± 1 beats min^{-1} and 74 ± 2 beats min^{-1} respectively; $P < 0.001$). When both drugs were used in combination, there was a significant decrease in pulse rate compared with lacidipine alone (58 ± 1 beats min^{-1} and 86 ± 1 beats min^{-1} respectively; $P < 0.001$).
- 4 Home blood pressure recordings confirmed the statistically significant reduction in blood pressure on co-dosing ($120/82 \pm 10/2$ mm Hg) compared with lacidipine ($140/92 \pm 5/3$ mm Hg) and atenolol ($146/90 \pm 6/3$ mm Hg) given alone ($P < 0.05$).
- 5 Lacidipine alone produced a significant exercise tachycardia compared with atenolol alone and the atenolol/lacidipine combination (97 ± 8 beats min^{-1} ; 65 ± 4 beats min^{-1} and 75 ± 7 beats min^{-1} respectively; $P < 0.001$). Exercise tolerance was not adversely affected by the co-administration of both lacidipine and atenolol.

Keywords lacidipine atenolol calcium antagonist hypertension pharmacokinetics pharmacodynamics interaction

Introduction

Lacidipine is a new calcium antagonist of the 1,4-dihydropyridine class which is effective as a once daily agent in the treatment of hypertension [1]. It is currently licensed for use in the treatment of hypertension in a number of European countries including Italy, France and Greece.

Calcium antagonists and selective beta adrenoceptor antagonists are amongst the most widely co-prescribed drugs in the treatment of cardiovascular diseases. The combination has specific haemodynamic advantages since the vasodilatory side effects of the calcium antagonists may be countered by the properties of the β -adrenoceptor antagonists [2]. Conversely the tendency for atenolol to increase peripheral resistance and reduce

cardiac output may be balanced by the vasodilatation and reflex increase in sympathetic tone induced by the calcium antagonist [3].

Greater reductions in blood pressure can be achieved by the concomitant use of atenolol with calcium antagonists than with either drug alone [4]. Moreover, the concomitant use of two drugs in modest dosage may result in fewer side effects than with high dose monotherapy, particularly if both drugs have complementary modes of action [5].

Lacidipine undergoes extensive first pass metabolism with considerable inter-subject variation. It is highly protein bound (>95%), primarily to albumin, but also to α_1 -acid glycoprotein. There are at least four principal

metabolites, possessing little or no pharmacodynamic activity [6].

Atenolol is a cardioselective β -adrenoceptor blocker which is hydrophilic, minimally protein bound and excreted almost entirely unchanged in the urine [7]. In common with other β -adrenoceptor antagonists, it reduces hepatic blood flow but its effect on hepatic microsomal enzyme activity, in particular, antipyrine clearance is less clear [8, 9].

This study was designed primarily to assess the potential interaction of lacidipine and atenolol. Secondary objectives included an assessment of the effect of the four treatment regimens on exercise tolerance and semi-automatic home blood pressure monitoring. It was also desirable to ascertain the effects of these two dose combinations in ameliorating dihydropyridine related side effects secondary to peripheral vasodilation and also those due to β -adrenoceptor blockade.

Methods

Study design and patients

The study design was of a randomised, double-blind, four way crossover type.

Twelve patients with mild to moderate hypertension were studied. Mild to moderate hypertension was defined as a documented repeated diastolic blood pressure of between 95–120 mm Hg (phase V), together with a mean sitting diastolic blood pressure (after 10 min rest) in this range at the end of a 2 week, single-blind, run-in period on atenolol 100 mg daily.

The selection criteria included: male or female patients between the ages of 21–65 years, with mild to moderate essential hypertension either newly presenting or not satisfactorily controlled on present monotherapy. Exclusion criteria included: any secondary form of hypertension, accelerated hypertension, ischaemic heart disease, congestive cardiac failure, cardiac conduction abnormalities, cerebrovascular disease and any other intercurrent disease.

All patients underwent physical examination, ECG and baseline blood tests prior to commencement of the study. Follow up assessments and a general enquiry as to the state of the patients' health were performed at the end of each 2 week period and also within 2 weeks of completion of the study.

Treatments

During the 2 week run-in period patients received atenolol 100 mg daily. Thereafter patients received, in a randomised double-blind four way crossover fashion, placebo once daily, atenolol 100 mg once daily, lacidipine 4 mg once daily and atenolol/lacidipine combination once daily for 14 days. All tablets were taken in the morning with the appropriate placebo tablets to maintain blindness.

On day 1 of the run-in period and on day 14 of each 2 week study period (including the run-in period) patients received their medication under supervision at the

research unit where they remained until at least 4 h post dosing. All other dosing was carried out at home and documented by the patient.

On day 14 of each treatment period patients returned to the unit having eaten a light breakfast at home. Caffeinated beverages were avoided on study days and patients were also asked to refrain from alcohol the night before dosing on day 14 and also to refrain from smoking for the first 4 h post-dosing. Patients were asked not to use any additional medications whilst enrolled in the study.

Blood pressure, pulse and exercise testing

Blood pressure was measured with a Hawksley Random Zero sphygmomanometer (diastolic-Korotkoff phase V) on day 14 of each treatment period. Sitting and standing blood pressure measurements were taken in duplicate after 3 min and 2 min rest respectively, pre-dose and at 2 h and 4 h post-dosing.

Home blood pressure recordings were obtained using the Copal UA 751 instrument [10], on days 1, 13 and 14, pre-dose and thereafter at two hourly intervals until bedtime on days 1 and 13 and until 4 h post-dose on day 14.

Pulse rate measurements at the unit were taken manually (radial artery), over 30 s immediately after each blood pressure recording (sitting and standing). Home pulse rate recordings were also obtained using the Copal UA 751 instrument.

Twelve lead ECG recordings were obtained on day 1 of the run-in phase and at each day 14 visit. During the run-in phase of the study, a 4-min submaximal exercise test was performed on a motor driven treadmill to establish the exercise load to be used after the 4 h cardiovascular measurements on day 14 of the subsequent treatment phases. The load was kept constant for each patient, having been determined during the run-in phase. Standing systolic blood pressure was measured immediately before exercise and again 15 s after completion. Exercise testing was performed at 4 h post-dosing as the maximal effect on heart rate and blood pressure of both drugs would still be apparent at this stage [6, 11]. Exercise endpoints were 4 min of exercise, heart rate more than 130 beats min^{-1} or inability of the patient to continue.

Assays

Blood samples were drawn on day 14, pre-dose, for determination of trough drug concentrations and 2 h post-dosing for peak concentrations (corresponding to the t_{max} of both atenolol and lacidipine) [6, 11]. Plasma atenolol concentrations were measured by solid phase extraction and high performance liquid chromatography (Bios Ltd, Surrey, England). The precision measured in terms of the coefficient of variation ranged from 1.4% at 100 ng ml^{-1} up to 7.5% at 10 ng ml^{-1} whilst the accuracy measured as a bias ranged from -5.3% at 10 ng ml^{-1} to +5.1% at 200 ng ml^{-1} . Plasma lacidipine concentrations were measured by high performance liquid chromatography (Glaxo S.p.A. Verona, Italy) with a quantitation limit of 0.5 ng ml^{-1} starting from 3.0 ml plasma and a precision of 13.6% at 3 ng ml^{-1} .

Adverse events

Patients were asked to report any adverse events if and when they occurred. Enquiries made as to whether the patient had experienced an adverse event were limited to a general question as to how the patient felt.

Statistics

Twelve patients providing evaluable data gave the study an estimated power of 80% to detect a mean difference in diastolic blood pressure of 7.1 mm Hg between any two treatment groups. This assumed that significance would be declared at the two-sided 5% level and that there would be no carry over from one period to the next.

The primary measure of response was the sitting diastolic blood pressure. Separate analyses of variance were performed on the data obtained pre-dose, 2 h and 4 h post-dose from day 14. Effects due to sequence, patients, periods and treatments were allowed for in the analyses. The effect of the atenolol/lacidipine combination was compared with the effect of atenolol alone and lacidipine alone.

Treatment comparisons were also made between placebo and atenolol and between placebo and lacidipine. The data obtained from the Copal recordings were not used for primary end-point analysis.

The study was approved by the joint ethics committee of Grampian Health Board and the University of Aberdeen.

Results

Blood pressure and pulse rate

The mean sitting diastolic blood pressure on day 14 of the run-in period was 104 mm Hg (range 96 mm Hg–111 mm Hg).

On day 14 of the subsequent atenolol treatment phase, the pre-dose mean sitting diastolic blood pressure was 95 mm Hg (range 84 mm Hg–112 mm Hg), with a lowest post-dosing mean value of 89 mm Hg (range 65 mm Hg–110 mm Hg) which occurred at 4 h post-dosing (Figure 1).

On lacidipine alone a mean pre-dose value of 96 mm Hg (range 81 mm Hg–152 mm Hg) for sitting diastolic blood pressure was found on day 14. The lowest mean value post-dosing was 83 mm Hg (range 60 mm Hg to 104 mm Hg) and occurred at 2 h post-dosing (Figure 1).

With co-dosing of atenolol and lacidipine, a mean value of 87 mm Hg (range 68 mm Hg–104 mm Hg) was seen on day 14 pre-dose. The lowest mean value post-dosing was 71 mm Hg (range 60 mm Hg–86 mm Hg) and also occurred at 2 h post-dosing (Figure 1).

On placebo, a mean value of 102 mm Hg (range 88 mm Hg–111 mm Hg) was seen on day 14, pre-dose, and was virtually constant for the 4 h post-dosing period (Figure 1).

Figure 1 Mean sitting blood pressures, systolic (upper) and diastolic (lower), pre-dose, 2 h and 4 h post-dosing on day 14, after placebo (▲), atenolol 100 mg (○), lacidipine 4 mg (●) and lacidipine/atenolol combination (□). For the purpose of clarity, graphs are slightly displaced to the right. Standard error bars included.

Similar results were found with regard to sitting systolic blood pressure (Figure 1). On inspection of the values obtained pre-dosing on day 14 of each period, again the lowest mean value was obtained with the combination and the highest after dosing with placebo. The greatest fall in blood pressure within the 4 h post-dosing period was evident after the co-administration (mean fall of 31 mm Hg evident at 2 h post-dosing). Lacidipine alone, resulted in the next largest fall (mean fall of 16 mm Hg evident at 2 h post-dosing), followed by atenolol alone (mean fall of 13 mm Hg, evident at 4 h post-dosing). Again dosing with placebo produced very little change with time.

A fall in standing blood pressure occurred after dosing with each drug alone, although generally a more marked response was evident following lacidipine (Figure 2). Co-dosing produced an additive effect. None of the reductions in blood pressure measured was associated with any adverse symptoms.

Sitting diastolic blood pressure at both 2 and 4 h post-dosing, showed a significant treatment effect ($P < 0.001$). The difference was seen between lacidipine and placebo (−15 mm Hg and −10 mm Hg at 2 and 4 h respectively; $P < 0.001$) and with the combination compared with both atenolol (−21 mm Hg and −10 mm Hg at 2 and 4 h respectively; $P < 0.001$) and lacidipine (−12 mm Hg and −10 mm Hg at 2 and 4 h respectively; $P < 0.001$). The difference between atenolol and placebo was significant at the 5% level, at 4 h post-dosing (−11 mm Hg reduction; $P = 0.001$) and approached signifi-

cance at the 2 h time point (-6 mm Hg reduction; $P = 0.062$). Furthermore analysis of sitting systolic and standing diastolic blood pressures all showed that the combination produced significantly greater reductions than those produced with either drug alone ($P < 0.01$).

Pulse rate

Statistically significant treatment effects were also found with regard to sitting and standing pulse rate (Figure 3). At 2 and 4 h post-dosing there was a significant increase in pulse rate with lacidipine (range of means 12–21 beats min^{-1}) compared with placebo ($P < 0.001$). Significant decreases in pulse rate were observed with atenolol (range of means 18–24 beats min^{-1}) when compared with placebo ($P < 0.001$) and also with the combination (range of means 28–38 beats min^{-1}) compared with lacidipine ($P < 0.001$).

Home blood pressure recordings

On inspection of the day 14 Copal data, there was overall general agreement with the Hawksley readings (Table 1). Thus there was a statistically significant reduction in blood pressure evident upon the co-dosing compared with each drug given alone ($P < 0.018$), and a statistically significant reduction in pulse rate, following the combination compared with lacidipine alone ($P < 0.001$). The day 1 data of the four treatment periods are more difficult to interpret, since a carry-over effect from the previous period was apparent on all occasions. This was not unexpected, given that there was no wash-out period between treatments.

Exercise testing

During the run-in phase on atenolol, seven of the twelve patients completed the 4 min exercise test, whilst treatment with atenolol during the study itself, resulted in nine of the ten tested patients successfully completing 4 min. The remaining two patients were not tested, one because of withdrawal from the study and one because of machine failure. Thus it can be seen that there was little overall difference between these two treatment periods with atenolol, as would be expected. Upon dosing with lacidipine, only four patients exercised for 4 min (Table 2). The remaining eight patients showed marked increases in pulse rate, within 1 to 3 min, which precluded continuation of the exercise test. All patients were asymptomatic. On co-administration, of the eleven patients for whom data were available, all but one successfully completed the 4 min exercise test. From the analysis comparing the combination with lacidipine alone, the differences with regard to the number of patients managing to complete the exercise test, together with the times to cessation of exercise were both significant ($P = 0.016$ and $P = 0.008$, respectively). Furthermore, diastolic blood pressure was significantly lower, post-exercise with the combination compared with either atenolol or lacidipine alone ($P = 0.039$ and $P = 0.011$, respectively). Systolic blood pressure was also significantly lower with the combination compared with atenolol alone ($P = 0.001$).

Figure 2 Mean standing blood pressures, systolic (upper) and diastolic (lower) pre-dose, 2 h and 4 h post-dosing on day 14, after placebo (▲), atenolol 100 mg (○), lacidipine 4 mg (●) and lacidipine/atenolol combination (□). For the purpose of clarity, graphs are slightly displaced to the right. Standard error bars included.

Figure 3 Mean sitting and standing heart rates, sitting (upper) and standing (lower) pre-dose, 2 h and 4 h post-dosing on day 14, after placebo (▲), atenolol 100 mg (○), lacidipine 4 mg (●) and lacidipine/atenolol combination (□). For the purpose of clarity, graphs are slightly displaced to the right. Standard error bars included.

Table 1 Sex, age, weight, adverse events and mean home blood pressure on day 13 of each treatment period for each patient

Patient	Sex	Age (years)	Weight (kg)	Adverse events	Home BP (mm Hg) (mean day 13)			
					(L)	(A)	(A/L)	(P)
1	F	49	80.2	Ankle swelling (A/L) Headache (A/L) (P) Nocturia (A/L)	122/84	155/105	119/84	142/102
2	F	60	70.9		151/87	172/103	148/88	177/103
3	M	48	75.0		126/87	116/78	110/72	141/95
4	M	59	88.9	Myocardial infarct (A) Facial flushing (L) (A/L) (P)	119/89	151/94	128/81	162/86
5	F	62	72.2		161/108	174/94	—	—
6	M	49	85.6		129/93	—	120/78	143/98
7	F	49	67.9		—	163/90	137/83	131/89
8	M	47	98.7		168/107	133/85	138/90	161/107
9	F	50	55.0		128/80	127/75	129/77	142/102
10	M	38	90.0		160/105	140/89	148/88	—
11	M	64	91.2		140/84	144/87	128/80	143/84
12	M	46	79.0		137/91	131/86	120/77	—
Mean		52	79.6		140/92	146/90	120/82	149/96
s.e. mean		2.2	3.5		5.2/3.0	5.7/2.8	9.9/1.7	4.8/2.7

L = Lacidipine, A = Atenolol, A/L = Atenolol and lacidipine combination, P = Placebo.

Table 2 Exercise tolerance, blood pressure and heart rate, 4 h post-dosing on day 14, of each treatment phase. (s) = exercise stopped

Patient	Duration (s)	BP (mm Hg)	HR (beats min ⁻¹)	Duration (s)	BP (mm Hg)	HR (beats min ⁻¹)
<i>Lacidipine 4 mg</i>				<i>Atenolol 100 mg</i>		
1	109 (s)	137/82	96	240	174/98	67
2	164 (s)	146/80	101	240	204/95	56
3	94 (s)	156/104	120	240	130/80	57
4	240	138/88	96	240	187/110	71
5	240	137/100	104	—	—	—
6	240	132/98	98	240	132/89	57
7	160 (s)	152/78	113	80 (s)	188/82	52
8	60 (s)	169/110	104	240	164/100	88
9	112 (s)	135/111	108	240	137/81	52
10	66 (s)	196/105	115	240	212/104	84
11	77 (s)	172/94	102	—	—	—
12	240	161/93	107	240	152/97	63
Mean	150	153/88	97	224	168/95	65
s.e. mean	21	5.6/7.8	7.9	16	9.4/3.2	4.0
<i>Lacidipine/atenolol</i>				<i>Placebo</i>		
1	240	124/80	75	110 (s)	159/76	80
2	240	146/80	72	235 (s)	191/97	93
3	240	118/64	58	240	138/90	98
4	240	136/86	73	240	181/97	86
5	—	—	—	—	—	—
6	240	149/104	69	240	160/120	76
7	240	148/66	65	76 (s)	183/111	88
8	75 (s)	133/84	133	40 (s)	170/108	82
9	240	150/80	64	120 (s)	168/100	99
10	240	183/109	94	102 (s)	184/118	100
11	240	143/76	72	94 (s)	227/99	112
12	240	128/84	55	240	144/117	97
Mean	225	142/83	75	158	173/103	92
s.e. mean	15	5.3/4.1	6.5	24	7.4/4.0	3.2

Drug assays

From the lacidipine pre-dose concentration data, there was no evidence that there had been any accumulation of lacidipine upon repeated dosing with the lacidipine/atenolol combination compared with lacidipine given

alone. The 2 h post-dosing data (Table 3) revealed no evidence for a significant change in the concentrations of lacidipine when prescribed with atenolol (lacidipine alone 3.39 ± 1.26 ng ml⁻¹ vs lacidipine/atenolol 3.018 ± 0.75 ng ml⁻¹; $P = 0.582$).

The 2 h post-dosing atenolol concentration data did

Table 3 Plasma lacidipine and atenolol concentrations (ng ml⁻¹), 2 h post-dosing, following administration of each drug alone and in combination

Patient	Lacidipine L (ng ml ⁻¹)	Lacidipine/Atenolol L (ng ml ⁻¹)	Atenolol A (ng ml ⁻¹)	Atenolol/Lacidipine A (ng ml ⁻¹)
1	5.8	6.0	276.7	251.4
2	5.4	4.8	791.9	1006.5
3	1.8	4.0	365.9	736.3
4	2.8	2.1	581.4	830.2
5	0.5	—	466.5	—
6	1.5	1.0	908.8	658.1
7	14.8	8.5	752.0	821.5
8	1.3	2.1	548.8	452.8
9	0.5	1.2	1068.4	1606.6
10	0.8	1.7	608.4	812.5
11	1.0	1.2	778.9	921.5
12	1.6	0.6	238.9	273.1
Mean ± s.e. mean	3.2 ± 1.2	3.0 ± 0.8	615.6 ± 73.6	761.0 ± 113.5

L = Lacidipine, A = Atenolol.

show a modest increase in atenolol concentration upon co-dosing but this was not statistically significant (atenolol alone 629.1 ± 79.2 ng ml⁻¹ vs lacidipine/atenolol 760.95 ± 113.5 ng ml⁻¹; $P = 0.075$). The trough concentrations did not differ significantly on the two dosing occasions.

Adverse events

A summary of documented adverse events is seen in Table 1. No significant biochemical or haematological abnormalities were observed during the study.

Discussion

Both lacidipine and atenolol were well tolerated with three patients experiencing adverse events. One of the patients was withdrawn from the study after receiving the last dose of atenolol because of new ECG changes diagnostic of an anterolateral sub-endocardial infarct which was asymptomatic.

Both atenolol and lacidipine alone produced a fall in sitting diastolic blood pressure and together produced a clinically and statistically significant additive effect. It would therefore appear that both these drugs may be safely co-administered in patients not responding satisfactorily to monotherapy.

Statistically significant changes in pulse rate were also elicited, with lacidipine increasing pulse rate and atenolol decreasing it. The combination of these drugs produced a pulse rate significantly lower than that seen with lacidipine alone. Exercise testing was assessed 4 h post-dosing as we anticipated the maximal effect of both drugs would be at 4 h. Our data showed the maximal effect of lacidipine to be at 2 h although almost as great an effect was seen at 4 h. Exercise tolerability was not adversely affected by the co-administration of both these drugs, but lacidipine alone, resulted in a significant exercise-induced tachycardia.

The higher sitting and standing heart rates on lacidipine are presumably the result of reflex tachycardia that accompanies the action of arteriolar vasodilator drugs. The co-administration of atenolol suppressed this.

Although the tachycardia itself did not result in adverse effects or symptoms in this small study, it may cause problems in some patients, resulting in palpitations and chest tightness. This may be overcome by the co-administration of a β -adrenoceptor antagonist, though it is far less clear if the other vasodilator effects of dihydropyridines can be prevented, such as headache, flushing and peripheral oedema.

The increase in heart rate during mild exertion while on lacidipine is more difficult to explain. This would be considered undesirable in patients with ischaemic heart disease until shown to be safe.

Finally, with regard to both blood pressure and pulse rate data, it is of interest to note that these results were in agreement with those produced using the Copal UA 751. The use of home blood pressure recordings may be of benefit in the evaluation of anti-hypertensive agents. Although in this study the Copal data confirmed what had been observed at clinic visits, the technique can be used to provide additional information about peak effects and duration of action. These aspects were not formally examined in this study, though inspection of the individual patient recordings suggested a peak action of lacidipine at 2 h and a duration of effect in the region of 10–14 h.

We were interested in a possible interaction between both drugs and therefore sampled at $t_{\max}$ (2 h) of both and 24 h post-dosing looking for an accumulative effect on either drug with co-administration. From the limited trough and peak concentrations obtained for the two drugs, it would appear that no important pharmacokinetic interaction occurs. The lack of an interaction is not unexpected because atenolol is excreted almost entirely unchanged in the urine whilst lacidipine is extensively metabolised by the liver.

In conclusion, this study shows that lacidipine and atenolol may be safely co-administered in patients with mild to moderate hypertension, who have failed to respond satisfactorily to dosing with atenolol alone during a run-in period. All doses were generally well-tolerated and modest falls in blood pressure occurred after dosing with each drug alone. There was a clinically and statistically significant additive effect on blood pressure reduction, evident upon co-administration.

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