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ORIGINAL ARTICLE

A randomised, double-blind, double-dummy comparison of the efficacy and tolerability of lercanidipine tablets and losartan tablets in patients with mild to moderate essential hypertension

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A double-blind, double-dummy, randomised, multicentre study to compare the efficacy and tolerability of lercanidipine with losartan. Patients with mild to moderate hypertension (supine diastolic blood pressure (DBP) 95–115 mm Hg) were enrolled and underwent a placebo run-in period of 14–30 days before random allocation to lercanidipine tablets 10 mg once-daily ($n = 234$) or losartan tablets 50 mg once-daily ($n = 231$) during the assessment period (approximately 16 weeks). Titration to lercanidipine 20 mg once-daily (two 10 mg tablets) or losartan 100 mg once-daily (two 50 mg tablets) was allowed after 8 weeks, if necessary. At the end of the study, 71% of patients who received lercanidipine tablets had achieved normalised DBP (ie, ⩽90 mm Hg) and 81% had responded to treatment (ie, DBP ⩽90 mm Hg or a decrease in DBP ⩾10 mm Hg). The corresponding numbers in the losartan tablets group were 65% and 78%, respectively. In those patients who required dose titration, there was evidence of a greater response with lercanidipine tablets than with losartan tablets. Both treatments were well tolerated with a low incidence of adverse drug reactions and a low withdrawal rate. In conclusion, the antihypertensive effects of lercanidipine tablets were comparable with those of losartan tablets; both treatments gave a high response rate for an antihypertensive monotherapy and were very well tolerated.
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Introduction

The British Hypertension Society guidelines recommend that a low dose thiazide diuretic should be used as first-line therapy in the management of hypertension.[1] The choice of second-line therapy depends on the indications and contraindications of the drugs and their efficacy and tolerability. There is an important role for the longer acting calcium channel blockers and drugs affecting the renin-angiotensin-aldosterone (RAA) system (ie, angiotensin II antagonists and angiotensin-converting enzyme (ACE) inhibitors) in the management of hypertension. This study aimed to provide an assessment of the comparative efficacy and tolerability of lercanidipine and losartan.

Lercanidipine is a dihydropyridine calcium channel blocker, which is effective in the treatment of mild to moderate essential hypertension and isolated systolic hypertension.[2,3] Lercanidipine has an unusual pharmacokinetic profile resulting from its high lipophilicity. It binds strongly to the lipid bilayer of cell membranes close to the calcium channel receptor from where it is slowly released over subsequent hours. This slow release from cell membranes gives a 24-h duration of pharmacological and therapeutic action despite the drug's short plasma half-life of approximately 2–5 hours.[4] Studies show that lercanidipine tablets are more effective than placebo in lowering blood pressure and are consistently as effective as other antihypertensive agents such as atenolol, hydrochlorothiazide, captopril, and slow-release nifedipine.[5–8]

Losartan potassium was the first angiotensin II receptor antagonist marketed in the UK. It was the first of a novel class of antihypertensive drugs that competitively and selectively block the angiotensin receptor sub-type 1 (AT_1 receptor). The efficacy of

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losartan tables 50–100 mg once-daily in mild to moderate hypertension was shown to be comparable with enalapril and atenolol in controlled clinical trials.[9] In a double-blind, parallel group study comparing the efficacy and tolerability of once-daily losartan tablets with the calcium channel blocker felodipine (extended release formulation), there were no statistically significant differences between the two treatments in terms of efficacy or tolerability at 6 and 12 weeks.[10] However, there was a trend throughout the study toward felodipine having a greater antihypertensive effect relative to losartan tablets.

This study was designed to compare the efficacy and tolerability of lercanidipine tablets with losartan tablets in the treatment of mild to moderate essential hypertension.

Materials and methods

Patients

This study was approved by the appropriate ethics committees and all the patients enrolled gave their written informed consent to take part. Patients were of either sex, aged 18–75 years with mild to moderate essential hypertension (ie, a supine diastolic blood pressure (DBP) 95–115 mm Hg, inclusive). Patients with mild to moderate essential hypertension that had not previously responded to two sequentially administered antihypertensives were excluded. Other major exclusion criteria included: severe hypertension (ie, a DBP >115 mm Hg); secondary hypertension; signs of postural hypotension; cardiac abnormalities (eg, angina pectoris, fixed cardiac output syndrome, valvular or congenital heart disease, cardiac arrhythmias, cardiomyopathy, sick sinus syndrome, second or third degree heart block, uncontrolled atrial fibrillation, and left bundle branch block); myocardial infarction, stroke, or transient ischaemic attack in the last 3 months; bradycardia or tachycardia (ie, heart rate <50 or >100 beats per minute); hypovolaemia; clinically significant hepatic or renal dysfunction; diabetes mellitus.

Methods

This was a randomised, double-blind, double-dummy, parallel group study carried out in general practice in the UK. Patients who were currently receiving antihypertensives had to stop taking them for the duration of the study and undergo a washout period of 14–20 days before entering the run-in period. All enrolled patients entered the run-in period, which lasted for 14–30 days. During this period, patients received placebo versions of both treatments in a single blind manner (ie, the investigator, but not the patient, was aware of the patient's treatment) and their blood pressure was assessed at each study visit (every 7 to 10 days). Patients had to have a DBP of 95–115 mm Hg at the start of the run-in period and at two visits during the run-in period to be eligible to enter the assessment period. Eligible patients were allocated to treatment according to a randomisation schedule.

The double-blind assessment period lasted for approximately 16 weeks (112–160 days). Patients received their allocated study medication and a placebo version of the alternative medication. They attended study visits at intervals of approximately 4 weeks (28–40 days). There were two dose levels of study medication. Level 1 was 10 mg lercanidipine tablets or 50 mg losartan tablets. Level 2 was 20 mg lercanidipine tablets (two 10 mg tablets) or 100 mg losartan tablets (two 50 mg tablets). All patients started treatment on level 1. Dose titration was allowed as follows:

- After approximately 8 weeks (56–80 days) in the assessment period, the investigator could increase an individual patient's dose from level 1 to level 2 if he/she had not responded to treatment (ie, achieved a supine DBP of ⩽90 mm Hg or a decrease in supine DBP of ⩾10 mm Hg).
- After approximately 12 weeks (84–120 days) in the assessment period, the investigator was able to increase a patient's dose from level 1 to level 2 if he/she had not normalised (ie, achieved a supine DBP of ⩽90 mm Hg) or decrease a patient's dose from level 2 to level 1 if he/she had experienced a severe adverse event caused by hypotension.

If a patient did not respond to treatment on level 2, no further dose increases were allowed, but the investigator had the option to withdraw the patient if he/she felt that the patient's blood pressure was not adequately controlled.

Investigators were given detailed instructions for measuring blood pressure. All the investigators used a standard mercury sphygmomanometer that had been calibrated in the last 12 months and the measurements had to be taken under standardised conditions, ie at approximately the same time of day at each visit, by the investigator or co-investigator, and using the same sphygmomanometer. The investigator measured the patient's blood pressure in the supine position (after the patient had been supine for at least 5 min) and standing (after the patient had been standing for 1 min). The investigator took two readings in each position and recorded both of these readings, together with the mean. If the two diastolic readings in the supine position differed from each other by more than 5 mm Hg, two further readings were taken. At the first visit, the investigator measured the patient's blood pressure in both arms and the arm with the highest reading was used for the rest of the study.

Statistics

It was estimated that, with 200 completing patients in each group, the study would have 90% power at

the 5% significance level to detect a 15% difference between treatments in the percentage of patients achieving normalised DBP.[5] Patients were sequentially allocated to treatment groups according to a computer generated randomisation list. The blind was not broken until after the initial statistical analyses had been carried out.

The statistical analyses were carried out using the available data; no measures were taken to replace missing data or to compensate for patients who withdrew.

The following parameters were compared between treatment groups using the χ^2 test: numbers of normalised and responding patients at the end of the assessment period; number and percentage of patients taking each of the two dose levels at the end of the assessment period; number of patients withdrawing from the study; number of normalised patients at the end of the study subdivided by age group (<55 years and ⩾55 years). Patients' pulse rate (radial pulse), and PR interval and heart rate from the ECG trace were compared between treatment groups using analysis of covariance (ANCOVA) with the baseline values as covariates.

Results

Patients

A total of 562 patients were enrolled, 519 entered the run-in period, and 465 entered the assessment period. Of the 97 patients who withdrew before the assessment period, 62 failed the continuation criteria (ie, did not have a DBP of ⩾95 mm Hg and <115 mm Hg at visit 1 and two other visits during the titration period), five withdrew because of AEs with/without 'other reasons', and 30 withdrew for 'other reasons' alone.

One hundred and nineteen patients (51%) in the lercanidipine tablets group and 123 (53%) in the losartan tablets group were male. With the exception of one patient in the lercanidipine tablets group and six in the losartan tablets group, all the patients were Caucasian. The two groups were comparable for mean age, height, weight, DBP, and systolic blood pressure (SBP) (Table 1). Ninety-nine patients (42%) in the lercanidipine tablets group and 112 (49%) in the losartan tablets group were smokers, the remaining patients were non-smokers or ex-smokers. Most patients had been diagnosed with hypertension at least one year before their entry into the study: 138 patients (59%) in the lercanidipine tablets group and 145 (63%) in the losartan tablets group.

Table 1 Baseline characteristics

	Lercanidipine tablets (n = 234)	*Losartan tablets (n = 231)*
Mean (s.d.):		
Age (years)	54.7 (10.9)	54.8 (9.8)
Weight (kg)	82.7 (17.3)	81.8 (16.2)
Height (cm)	168.5 (9.7)	168.3 (9.4)
Supine DBP (mm Hg)	101.9 (4.9)	102.6 (5.2)
Supine SBP (mm Hg)	165.6 (15.7)	164.9 (14.4)

Table 2 Reasons for withdrawal during the assessment period

	Number (%) of patients	
	Lercanidipine (n = 234)	*Losartan (n = 231)*
AE	17 (7)	8 (3)
Lack of efficacy	11 (5)	12 (5)
Other	6 (3)	6 (3)
AE and other	1 (<1)	2 (1)
Total	35 (15)	28 (12)

During the assessment period, 35 of the 234 patients (15%) receiving lercanidipine tablets and 28 of the 231 patients (12%) receiving losartan tablets withdrew (Table 2). The difference between treatment groups was not statistically significant ($P = 0.372$).

Blood pressure

The percentages of patients who achieved normalised DBP (ie, supine DBP ⩽90 mm Hg) or responded to treatment (ie, supine DBP ⩽90 mm Hg and/or a decrease in supine DBP ⩾10 mm Hg) increased between 8 weeks and the end of the study (16 weeks) in both groups (Figure 1). At the end of the study, 71% of patients in the lercanidipine tablets group and 65% in the losartan tablets groups had achieved normalised DBP and approximately 80% in both groups had responded to treatment. The differences between the treatment groups at the end of the study were not statistically significant ($P = 0.214$ for normalised patients and $P = 0.380$ for responding patients). When the data for the percentage of patients who achieved normalised DBP were summarised by mean age groups (ie, patients aged <55 years and those aged ⩾55 years), there were no stat-

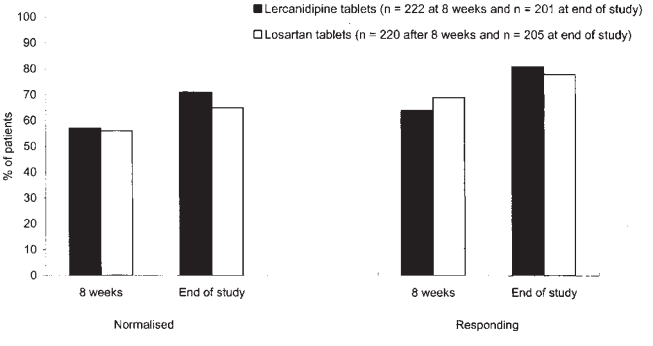

Figure 1 Percentage of patients normalised (DBP ⩽90 mm Hg) and responding to treatment (DBP ⩽90 mm Hg or decrease in DBP ⩾10 mm Hg).

istically significant differences between the treatments for either age group.

Approximately half the patients in the lercanidipine tablets group (104 patients; 51%) were titrated from 10 mg to 20 mg during the assessment period. In the losartan tablets group, 92 patients (45%) were titrated from 50 mg to 100 mg. The difference between the treatments in the number of patients receiving each dose level was not statistically significant ($P = 0.182$). Most of the patients who had their dose increased were titrated after approximately 8 weeks' treatment. The number of normalised patients in each treatment group at the end of the study was summarised by dose level (Figure 2). At level 1, the percentage of normalised patients was the same in both groups (ie, 85%), but at level 2, the percentage of normalised patients was greater in the lercanidipine tablets group (57%) than in the losartan tablets group (40%).

Both treatments gave decreases in supine and standing DBP and SBP between the end of the run-in period and the end of the study (see Table 3). The changes from supine to standing measurements showed that patients' DBP increased slightly and their SBP decreased slightly on standing. There was no evidence of postural hypotension.

Pulse rate and ECG

In the lercanidipine tablets group, the mean (s.d.) pulse rate was 75.3 (8.3) beats per minute (bpm) at the end of the run-in period and 79.5 (12.2) bpm at the end of the study. The corresponding values in the losartan tablets group were 73.9 (8.8) bpm and 74.1 (10.0) bpm, respectively. The treatment difference at the end of the study was statistically significant ($P < 0.001$).

Table 4 shows the results for the PR interval and heart rate from the ECG trace at entry into and at the end of the study for patients in both groups. The results for the heart rate corresponded with the data recorded for the pulse rate. There was evidence of an increase in the PR interval for patients who received losartan tablets. At the end of the study, both the PR interval and heart rate were statistically significantly different between treatments ($P = 0.015$ and $P < 0.001$, respectively).

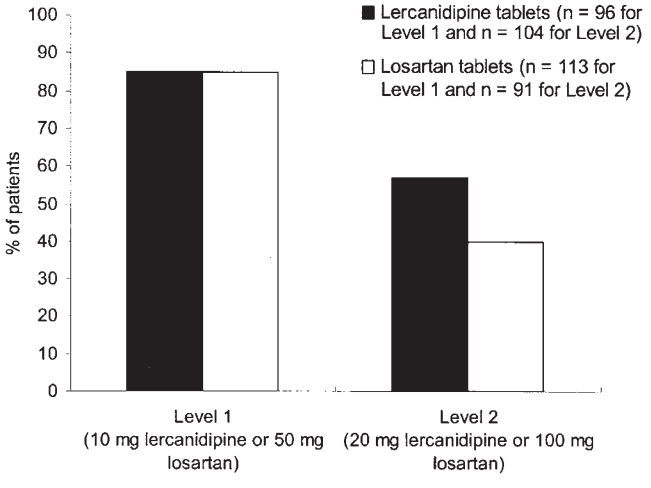

Figure 2 Percentage of patients normalised (DBP ≤90 mm Hg) at the end of the study by dose level.

Table 3 Supine and standing DBP and SBP

	Mean (s.d.) diastolic blood pressure (mm Hg)	
	Lercanidipine tablets (n = 234)	*Losartan tablets (n = 231)*
SBP (mm Hg)		
Supine:		
End of run-in	162.9 (15.0)	161.9 (13.3)
End of study	147.8 (15.5)	143.6 (15.1)
Standing:		
End of run-in	162.2 (14.8)	160.7 (12.7)
End of study	147.6 (16.3)	143.5 (15.5)
DBP (mm Hg)		
Supine:		
End of run-in	100.7 (4.5)	101.4 (4.9)
End of study	88.0 (7.1)	88.4 (7.5)
Standing:		
End of run-in	103.3 (6.3)	103.1 (5.9)
End of study	91.1 (8.6)	91.5 (8.6)

Table 4 ECG parameters

	Mean (s.d.)			
	Lercanidipine tablets		*Losartan tablets*	
	Entry (n = 234)	*End of study (n = 204)*	*Entry (n = 231)*	*End of study (n = 208)*
PR interval (ms)	160.9 (28.4)	159.2 (26.2)	162.2 (26.9)	165.5 (26.5)
Heart rate (bpm)	73.5 (11.2)	79.5 (14.2)	72.2 (10.7)	72.8 (11.4)

Adverse drug reactions

During the assessment period, 80 patients (34%) receiving lercanidipine tablets and 69 (30%) receiving losartan tablets reported at least one adverse drug reaction (ie, an adverse event that was considered, by the investigator, to be related to treatment). Headache and dizziness were the most commonly reported adverse drug reactions. Sixteen patients (7%) receiving lercanidipine tablets and 22 patients (10%) receiving losartan tablets reported headache. Eighteen patients (8%) receiving lercanidipine tablets and 11 (5%) receiving losartan tablets reported dizziness. All other adverse drug reactions were reported by less than 5% of patients. The inci-

dence of peripheral oedema was very low in both groups: seven patients (3%) in the lercanidipine tablets group and three (1%) in the losartan tablets group.

There were two deaths during the study; in both cases, the investigator concluded that the deaths were improbably related to the study medication. One patient died on the day after being withdrawn from the run-in period (cause of death was given as coronary atherosclerosis and ischaemic heart disease). A second patient died during the assessment period while receiving lercanidipine tablets. This patient died suddenly while on holiday abroad. The available information indicated that he had suffered an asthma attack (the patient had a history of chronic obstructive pulmonary disease).

Compliance

Compliance during the study was excellent. Based on tablet counts of returned medication, over 97% of patients in both groups took at least 90% of their scheduled doses.

Discussion

Both treatments were effective in controlling patients' DBP as shown by the percentage of normalised and responding patients. The high percentage of normalised patients at the end of the study (71% in the lercanidipine tablets group and 65% in the losartan tablets group) is an encouraging result for an antihypertensive monotherapy even when the study exclusion criteria are considered. Based on data collected in previous clinical trials, the British Hypertension Society recognise that over half of all hypertensive patients will need more than one drug and approximately one-third will need three or more drugs to control their hypertension.[1]

There was evidence for a better dose response with lercanidipine tablets than with losartan tablets. Of those patients who were titrated to dose level 2, a higher percentage was normalised with lercanidipine tablets than with losartan tablets. Most of the patients who were titrated to the higher dose level had their dose changed after approximately 8 weeks' of treatment. Studies have shown that during treatment with lercanidipine tablets, patients' blood pressure continues to fall up to 4 to 5 months after starting treatment.[11] It is therefore probable that a dose increase was unnecessary for some patients.

Postural hypotension is a problem with short-acting dihydropyridine calcium channel blockers such as nifedipine. Based on the blood pressure measurements taken at each study visit, there was no evidence of postural hypotension with either treatment in this study. The changes between supine and standing blood pressure measurements showed a slight increase in the DBP and a slight decrease in the systolic pressure, which is as expected.

The lack of a placebo arm is a drawback for the analyses of the results of this study, but it was not considered ethical to treat patients with placebo for the duration of the study. In addition, both lercanidipine and losartan have previously been shown to be significantly more effective than placebo.[12,13]

The overall incidence of adverse drug reactions was low with both treatments and only headache and dizziness were reported by more than 5% of patients. Peripheral oedema is a common problem with some dihydropyridine calcium channel blockers, but in this study there was a very low incidence of this side effect with lercanidipine tablets. It is known that peripheral oedema can take time to develop, but during 12 months of treatment with 10 mg lercanidipine in a previous study only 1.4% of patients had ankle oedema.[11] In addition, a study by Borghi *et al*[14] showed that peripheral oedema may affect fewer patients with lercanidipine than with other dihydropyridines. In this study, a group of 115 hypertensive patients currently being treated with amlodipine, nifedipine GITS, nitrendipine, or felodipine were switched to treatment with lercanidipine (10–20 mg/day) for 4 weeks and then re-challenged with their original treatment for a further 4 weeks. With their original treatment, 94.8% of patients had ankle oedema. The incidence decreased to 51.4% after 4 weeks of treatment with lercanidipine ($P < 0.001$ *vs* the original treatment) and increased to 90.1% when patients were re-challenged with their original treatment ($P < 0.001$ *vs* lercanidipine).

The number of patients withdrawing for adverse events was higher in the lercanidipine group than in the losartan group, but the numbers were small and the overall withdrawal rate was not statistically significantly different between the groups.

At the end of the study, patients receiving lercanidipine tablets had a statistically significantly higher pulse rate and heart rate than patients receiving losartan tablets ($P < 0.001$). However, the mean value in both treatment groups was between 70 and 80 bpm, which is accepted as normal. There was evidence for an increase in the PR interval with losartan tablets and the PR interval at the end of the study was statistically significantly longer for patients receiving losartan tablets than for patients receiving lercanidipine tablets. However, the mean values for both treatments were well within the normal limits (ie, 120–220 ms).[15]

The results of this study support those of previous studies described in abstracts, which have reported that lercanidipine tablets 10 mg may be as effective as candesartan[16] and more effective than irbesartan.[17]

In conclusion, the antihypertensive effects of lercanidipine tablets are comparable with those of losartan tablets and both treatments gave a high response rate for antihypertensive monotherapy. Both treatments were very well tolerated and neither had any clinically significant effects on cardiac conduction or heart rate.

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