Assessment of cognitive function in patients with essential hypertension treated with lercanidipine

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Objectives: The aim of this longitudinal, open-label, comparative, multicenter study was to assess cognitive function in hypertensive patients receiving mid-term treatment with lercanidipine.

Methods: Hypertensive patients aged 40 years or older were treated with lercanidipine (10 mg daily) after 7–10 days washout period. The duration of the study was 6 months. Blood pressure (BP) was measured every 4 weeks (JNC 6th report). In patients with inadequate BP control, doxazosin was added and up-titrated. At baseline and after 6 months of treatment, cognitive function was evaluated using the Spanish validated version of the Mini-Mental State Examination (MMSE) and the Trail Making Test (TMT).

Results: In the study population of 467 patients, BP decreased from 154.4/95.3 mmHg at baseline to 134.8/80.7 mmHg at 6 months. At the end of the study, 98% of patients were receiving lercanidipine, 20% an angiotensin-converting enzyme inhibitor, and 6% doxazosin. Adequate BP control was obtained in 68% of patients. The mean (standard deviation) MMSE scores improved from 32.35 (2.59) to 33.25 (2.36) ($p<0.0001$). Patients with good BP control scored significantly better than those with inadequate BP control ($p<0.05$), which was already observed at the first month.

Conclusions: The third-generation calcium channel antagonist, lercanidipine, improved cognitive function after 6 months of treatment especially in patients with good BP control, suggesting that improvements in cognitive function may be associated with a decrease in BP.

Keywords: lercanidipine, hypertension, cognitive function

Introduction

High blood pressure is a major risk factor for stroke and ischemic heart disease. The fact that hypertension increases with age may account for the expected increase in the incidence of acute cerebrovascular events and coronary artery disease in Western countries. On the other hand, dementia (Skoog et al 1996) and cognitive impairment (Kilander et al 1998) have been increasingly related to hypertension. It has been shown that hypertension precedes vascular dementia and Alzheimer-like dementia (Forette et al 1998). In this respect, some studies provided evidence that, in contrast to previous findings, antihypertensive treatment can prevent or delay the onset of dementia (Forette et al 2002). However, there is some controversy about the current information on whether the type of antihypertensive treatment used has an influence on the level of improvement in the cognitive function. The recently published Study on Cognition and Prognosis in the Elderly (SCOPE) (Lithell et al 2003) did not find any differences between a treatment based on an angiotensin-II receptor antagonist and an antihypertensive treatment that did not involve this drug class. To date, no studies have been published directly investigating cognitive function with third-generation calcium channel antagonists.

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Lercanidipine is a vasoselective dihydropyridine calcium channel antagonist that causes systemic vasodilation by blocking the influx of calcium ions through L-type calcium channels in cell membranes. It is a highly lipophilic drug that exhibits a slower onset and longer duration of action than other calcium channel antagonists. Furthermore, lercanidipine may have antiatherogenic activity unrelated to its antihypertensive effect. In two large, non-blind, non-comparative studies involving approximately 16 000 patients with mild to moderate hypertension, systolic blood pressure (SBP) and diastolic BP (DBP) were significantly reduced after 12 weeks' treatment with lercanidipine 10–20 mg/day (Bang et al 2003). The purpose of this study was to assess cognitive function by means of two tests evaluating cognitive disorders and psychomotor speed in patients with essential hypertension receiving mid-term treatment with lercanidipine, a third-generation calcium channel blocker.

Patients and methods

This was a longitudinal, open-label, comparative, multicenter study, which was designed to determine the effect of antihypertensive treatment with lercanidipine on cognitive function. Eligible patients were treated with lercanidipine with the possibility of adding an angiotensin-converting enzyme (ACE) inhibitor and doxazosin when adequate BP control with lercanidipine monotherapy was not achieved. The duration of the study was 6 months and was conducted in the primary care setting.

Male and female patients aged ≥40 years with newly diagnosed essential hypertension (SBP ≥140 mmHg, DBP ≥90 mmHg in non-diabetic subjects; SBP ≥135 mmHg, DBP ≥85 mmHg in patients with diabetes mellitus) or need to change the current medication for those subjects treated with antihypertensive drugs as monotherapy who were not managed according to guidelines of the 6th report of the Joint National Committee (National High Blood Pressure Education Program 1997) were eligible. The following exclusion criteria were applied: current treatment with lercanidipine and/or an ACE inhibitor and/or doxazosin; presence of secondary hypertension, symptomatic heart disease, organic cognitive impairment, serum creatinine concentration >1.7 mg/dL, venous insufficiency of the lower limbs, inability to complete the Mini-Mental State Examination (MMSE) (baseline MMSE score <27 for patients aged ≥60 years, and <24 for patients aged ≥61 years), as well as any contraindication for prescribing treatment with lercanidipine as considered by the investigator. Pregnant women, nursing mothers, or women of childbearing potential not using adequate methods of contraception were also excluded. Written informed consent was obtained from all participants.

Readings of SBP and DBP were taken with a sphygmomanometer with the patient seated in a chair with back supported, after 10 minutes of quiet rest. A visit blood pressure was the average of two separate measurements taken by the examining physician (a third measurement was obtained when there was a difference of 5 mmHg between the two readings). Adequate control of blood pressure was defined as SBP ≤140 mmHg and DBP ≤90 mmHg for non-diabetic patients, and SBP ≤135 mmHg and DBP ≤85 mmHg for patients with diabetes (National High Blood Pressure Education Program 1997).

The study medication was dispensed at the baseline visit. The daily dose was one tablet of lercanidipine (Zanidip®, Recordati España, San Sebastián de los Reyes, Madrid), 10 mg, taken with a glass of water immediately after breakfast. In previously treated hypertensive patients, a washout period of 7–10 days was required. Patients were assessed at baseline and at 4, 8, 12, 16, 20, and 24 weeks after commencement of treatment with lercanidipine. At each visit, blood pressure and heart rate were measured, and compliance with treatment was checked. During the clinic visits, study therapy could be uptitrated by adding a second antihypertensive drug (ACE inhibitor) and third antihypertensive drug (doxazosin) if blood pressure was still not controlled. The ACE inhibitor treatment was left to the treating physician. The same dose of lercanidipine was given throughout the 6-month study period. Treatment with doxazosin was started with a single daily dose of 2 mg, taken at night, followed by increases up to 8 or 16 mg daily if adequate control of BP was not achieved. Routine laboratory tests, including complete blood cell count, serum glucose concentration, liver and renal function tests, lipid profile, and ionogram were performed at baseline (visit 1) and after 6 months of treatment (visit 7). The body mass index (BMI) was also calculated. Obese patients were those with BMI ≥30 kg/m^2.

Cognitive function was assessed at baseline (visit 1) and at the end of the study (visit 7) using the MMSE and the Trail Making Test A (TMT-A) (Reltan 1959). The MMSE is used as a screening tool for the detection of cognitive disorders (Folstein et al 1975) and the TMT-A evaluates attention, concentration and psychomotor function. The MMSE is a widely used, well-validated screening tool for evaluation of cognitive impairment (Kukull et al 1994). It briefly measures orientation to time and place, immediate

recall, short-term verbal memory, calculation, language, and construct ability. In this study, the Spanish validated version of MMSE was used (Lobo et al 1999). It should be noted that the Spanish version of MMSE has a score of between 0 and 35. The TMT-A involves drawing a line to link a series of numbered dots that have been distributed over a sheet of paper. The score is obtained by measuring the time (in seconds) it takes the patient to complete the test and the number of mistakes made. In order to prevent test/re-test improvement in MMSE and TMT-A, patients were not told about correctness (incorrectness) or the interpretation of scores obtained either before or after testing. In the two tests, patients were questioned by a trained investigator.

Statistical analysis

Categorical data are expressed as absolute numbers and percentages and continuous data as mean and standard deviation (SD). In order to study differences in the quantitative variables over time as well as progression, or between group differences, the analysis of variance (ANOVA) for repeated or independent measurements was used. Categorical data were analyzed with the chi-square (χ^2) test for independent samples or the McNemar's test for paired samples. The relationship between results of the MMSE and the patient's age and BMI was assessed with the Pearson product-moment correlation coefficient (r). Statistical significance was set at $p<0.05$. The Statistical Analysis Systems (SAS Institute, Cary, NC, USA) statistical software package for Windows was used to analyze the data.

Results

Of the 544 patients who agreed to take part in the study, 77 (14.1%) were excluded for the following reasons: MMSE score at baseline lower than that required for entry (n=66), lack of compliance with treatment (n=10), and violation of the BP inclusion criterion (n=1). Therefore, the study population included 467 patients (67% males) aged between 42 and 79 years (mean 61.1±8.3 years). Fifty-six percent of patients were older than 60 years of age.

At the end of the study, 98.8% of patients were under treatment with lercanidipine, 20% had an ACE inhibitor added, and 6.1% doxazosin. Seventy-eight percent of patients received lercanidipine as monotherapy and 20% combined with the ACE inhibitor and doxazosin.

The mean BP of 154.4/95.3 mmHg at baseline decreased to 134/80.7 mmHg after 6 months of treatment. SBP decreased by 11.8% and DBP by 15.2%. These differences were statistically significant ($p<0.01$). Changes of BP readings during the study period are shown in Table 1. The overall percentage of patients with adequate control of BP was 68.3%. The percentage of patients with adequate control of BP was 82.7% in those younger than 60 years of age compared with 54.9% in patients with 60 years or more. However, BP readings at baseline were significantly higher in the older age group (161.3/94.5 mmHg vs 145.3/96.2 mmHg, $p<0.01$). On the other hand, the percentage of patients with adequate BP control was significantly higher in non-obese patients (BMI $<30\,kg/m^2$) than in obese subjects (BMI $\geq 30\,kg/m^2$) (70.3% vs 51.1%, $p<0.01$), as well as in patients treated with lercanidipine monotherapy than in those given lercanidipine in combination with an ACE inhibitor and doxazosin (74.7% vs 49.2%, $p<0.01$).

Significant variations in pulse rate and laboratory parameters between values at visits 1 and 7 were not observed.

The mean MMSE score at the beginning of the study (baseline) was 32.35±2.59 points, which increased significantly at the final visit with a mean score of 33.25±2.36 ($p<0.0001$). As compared with baseline, a statistically significant ($p<0.0001$) decrease in the seconds

Table 1 Changes of blood pressure and heart rate during the 6-month study period

Visits	Percentage of patients treated with			SBP mmHg[a]	DBP mmHg[a]	Heart rate beats/min[a]
	Lercanidipine	ACE inhibitor	Doxazosin			
Baseline	**0**	**0**	**0**	**154.4 (14.4)**	**95.3 (6.3)**	**74.7 (9.1)**
15 days	100	0	0	147.4 (12.1)	91.2 (6.3)	75.3 (8.2)
1 month	99	14	0	142.2 (10.7)	87.7 (6.5)	75.2 (8.2)
2 months	98	19	3	139.4 (9.5)	85.2 (6.3)	74.8 (7.9)
3 months	98	20	4	137.9 (9.5)	83.4 (6.1)	74.7 (7.7)
4 months	98	20	6	136.5 (8.8)	82.5 (6.3)	74.6 (7.6)
5 months	98	20	6	135.3 (8.1)	81.6 (5.9)	74.1 (7.4)
6 months	98	20	6	134.8 (8.1)	80.7 (5.5)	74.1 (7.2)

[a]Data as mean and standard deviation (SD).

Abbreviations: ACE, angiotensin-converting enzyme; DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 2 Results of the Mini-Mental State Examination (MMSE) according to whether adequate control of blood pressure was achieved

Patients without adequate BP control		Patients with adequate BP control	
Visit, no. patients	**MMSE score, mean (SD)**	**Visit, no. patients**	**MMSE score, mean (SD)**
Baseline, n=467	33.25 (2.36)	Baseline, n=467	33.25 (2.36)
15 days, n=400	33.23 (2.37)	15 days, n=16	33.69 (1.91)
1 month, n=316	33.12 (2.42)	1 month, n=97	33.66 (2.13)[a]
2 months, n=236	32.81 (2.59)	2 months, n=174	33.82 (1.89)[b]
3 months, n=187	32.63 (2.67)	3 months, n=224	33.74 (1.95)[b]
4 months, n=172	32.47 (2.70)	4 months, n=238	33.79 (1.92)[b]
5 months, n=140	32.43 (2.60)	5 months, n=239	33.66 (2.12)[b]
6 months, n=131	32.31 (2.54)	6 months, n=281	33.67 (2.15)[b]

[a]p=0.48 and [b]p<0.0001 compared with patients with adequate blood pressure (BP) control.

required to complete the TMT-A (76.20±58.77 vs 64.14±38.70s) and in the number of mistakes (2.82±2.70 vs 1.79±1.36) recorded at the final visit was also observed. In addition, there was a statistically significant inverse correlation between MMSE scores and patient's age ($r = –0.529$, $p<0.001$), that is, the younger the patient, the better the MMSE score. In fact, at the end of treatment subjects younger than 60 years scored significantly higher than those older than 60 years (34.43±1.37 vs 32.14±2.55, $p<0.0001$). No significant correlation was found between MMSE score and obesity ($r = –0.056$, $p=0.25$). On the other hand, there were no significant differences in the mean MMSE score at the end of the study regarding the use of lercanidipine as monotherapy or in combination (33.3±2.41 vs 33.09±2.22). The ANOVA analysis for the MMSE showed significant differences in the test scores between patients with adequate BP control and those in whom adequate control was not achieved (Table 2). In patients with adequate control of BP, the final MMSE score was 33.67±2.15 compared with 32.31±2.54 in patients without adequate BP control. In patients without BP control, MMSE score decreased from 33.25±2.36 at baseline to 32.31±2.54 at the end of the study.

Discussion

Firstly, this study shows that lercanidipine was efficient for controlling BP in 68% of a population of hypertensive patients who were either previously uncontrolled or who were just starting pharmacological therapy. The safety profile was excellent: at the end of the study, 98% of patients were still on lercanidipine treatment. Secondly, it has been observed that lercanidipine has a beneficial effect on the MMSE-measured cognitive function after 6 months of treatment. This is especially significant in those subjects with controlled BP, which suggests that the improvement of the cognitive function may be associated with a decrease in BP.

Despite all the campaigns that have been launched in the last three decades to improve control of hypertension, this is achieved in only a small proportion of hypertensive patients. Stroke rate (age-adjusted) has increased slightly since 1993, the reduction of ischemic heart disease has slowed down, and heart failure and progressive renal failure have increased. In the late 1990s, strict BP control did not even reach 30% of cases, with figures of only 27% in the United States (American Heart Association 1998), 24% in France (Chamontin et al 1998), 16% in Canada (Joffres et al 1997), 6% in the United Kingdom (Colhoun et al 1998), and 16.3% in Spain (Coca Payeras 1998; Barrios et al 2002). However, the situation has somewhat improved as a result of the introduction of newer and safer antihypertensive medications and to greater awareness of the importance of adequate BP control among healthcare professionals and the general population. Unfortunately, adequate BP control is still to be achieved in more than half of hypertensive patients.

The present results show that a therapeutic regimen with a third-generation dihydropyridine, such as lercanidipine, achieves BP control after 6 months of treatment in 68.3% of the patients, which is considerably higher than the average rates obtained with other current antihypertensive regimens. This is even more remarkable considering that, at the end of the study, 78% of patients were receiving lercanidipine as monotherapy, and in this subset of patients, BP control was achieved in 74.7% of them. We found that BP control was poorer in obese hypertensive subjects, although adequate BP control was obtained in 51% of these patients. Control of BP in obese hypertensive patients is even more significant if we take into account that long-term weight

reductions are not achieved in 80% of the cases. It is equally important to see how BP control is achieved in 82.7% of patients under 60 years of age, whereas in patients of 60 years or older, BP control was obtained in 54.9% of patients probably in relation to higher baseline SBP values in this group.

There is increasing evidence that high blood pressure can contribute to the development of cognitive function impairment and the onset of dementia (Launer et al 1995; Glynn et al 1999; Guo et al 1999). However, there is no general consensus on the mechanism whereby this occurs. In an analysis of the Framingham study, it was observed that a 12- to 15-year follow-up revealed impairment in the cognitive function in later years in untreated patients with high SBP and DBP (Farmer et al 1990; Elias et al 1993). Stratification by age showed a tendency to better cognitive function in subjects over 75 years of age if they had no isolated systolic hypertension or diastolic hypertension. The follow-up was extended to a 20-year observation period that showed a strong relationship between cognitive dysfunction and untreated hypertensive subjects compared with the hypertensive treated group. In the Honolulu study, a 25-year follow-up further emphasized the association between middle age systolic BP and cognitive impairment in later years (Launer et al 1995). This association between elevated systolic BP levels (and pulse pressure) and impairment in cognitive function could be anatomically reflected as brain atrophy (den Heijer et al 2003) and especially with white matter lesions (de Leeuw et al 2002). Therefore, it seems logical to believe that reducing BP by providing antihypertensive therapy may protect against development or onset of cognitive function impairment and dementia.

In one of the first large studies in which the impact of antihypertensive treatment on cognitive function was evaluated, the SHEP study on systolic hypertension in the elderly, no beneficial or deleterious effect was observed on cognitive function (Applegate et al 1994). However, the Syst-Eur study, published subsequently, which also investigated systolic hypertension in the elderly but had a different drug regimen, supported the hypothesis that antihypertensive treatment could be beneficial for cognitive function (Forette et al 1998). Treatment of systolic hypertension in elderly subjects with no previous dementia reduced the risk of developing dementia and Alzheimer's disease. In another study, the Kungsholmen study (Vitanen et al 1998) antihypertensive therapy reduced incidence of later development of dementia. In the Rotterdam study, for which more than 7000 hypertensive elderly subjects were included, the risk for dementia, particularly for the vascular type, was reduced by 30% in those patients who were receiving antihypertensive treatment (In't Veld et al 2001). This reduction was important but not significant, unlike the differences observed in the Syst-Eur and Kungsholmen studies (Forette et al 1998; Vitanen et al 1998). Antihypertensive treatment seems to be associated with a decrease in cerebral white matter lesions especially in the subcortical and paraventricular regions (Liao et al 1996; Dufouil et al 2001). These are the regions that appear to be associated with cognitive function impairment, although the relationship is unclear. Recently, Paran et al (2003) found poorer cognitive function in the presence of lower blood pressure and observed that mild hypertension improves cognitive function.

The discrepancies found among some of these studies, regarding the beneficial effect of antihypertensive treatment on global cognitive function, should be explained by the designs of different studies, their sample sizes, the different tests and methods used to assess cognitive function and to define dementia, and by the fact that cognitive function has been a secondary endpoint in most reports. However, the type of therapy used to treat hypertension could have contributed these inconsistencies in the results obtained. Overall, the effect that the type of antihypertensive treatment may have on cognitive function has been assessed in over 58 clinical studies. More than 8000 patients on diuretics have been investigated in 13 studies; most of them were receiving thiazide diuretics (Solomon et al 1983; Lasser et al 1989; Schmidt et al 1989; Bird et al 1990; Goldstein et al 1990; Cushman et al 1991; Nikolaus et al 2000; Ogihara and Kuramoto 2000). In most studies, diuretics were administered in combination with other drugs, whereas few studies analyzed the effect of diuretics as monotherapy. In general, these studies seem to indicate that diuretics neither improve nor aggravate cognitive function. Beta-blockers were investigated in 19 studies involving 13 000 subjects. No changes in cognitive function seem to take place with this type of therapy, although some worsening has been reported with propranolol and slight improvements were seen with beta 1-selective blocking agents. However, it is generally accepted that these drugs do not have a positive effect on cognitive function (Madden et al 1986, 1988; Steufert et al 1988; Palac et al 1990; Steiner et al 1990). ACE inhibitors have been evaluated in 9 studies including a population of somewhat over 9000 hypertensive patients. A positive influence on cognitive function was observed in these studies, especially on cognitive function impairment

of vascular etiology, which was more favorable that the effect obtained with diuretics and beta-blockers (Ameiling et al 1991; Frimodt-Moeller et al 1991).

The effect of calcium channel antagonists have been analyzed in 13 studies involving a population of approximately 10 000 hypertensive patients. The drug classes investigated were dihydropyridine calcium channel antagonists and, to a lesser extent, verapamil and diltiazem (Scarzella et al 1989; Leonetti and Salvetti 1994; Maxwell et al 1996; Palmer et al 1990; Ogihara et al 1992; Bulpitt et al 2000). Most data on dihydropyridines (nitrendipine) were obtained in the Syst-Eur study (Forette et al 1998). It has been generally shown that calcium channel antagonists improve cognitive function and reduce the incidence of vascular dementia. However, nifedipine compared with atenolol may subtly impair learning and memory in some elderly hypertensive patients (Skinner et al 1992). Improvement of cognitive function obtained with calcium channel antagonists seems to be similar or even higher than with other antihypertensive agents (Staessen et al 1998; Forette et al 2002). These drugs may prevent the onset of dementia not only in hypertensive subjects, but also in normotensive individuals (Maxwell et al 1996).

Studies on angiotensin-II receptor antagonists with losartan and valsartan have shown an improvement in cognitive function with the use of these antihypertensive drugs (Soma et al 1998; Tedesco et al 1999; Fogari et al 2003, 2004). No improvement was observed with candesartan in the recently published SCOPE study (Lithell et al 2003). The SCOPE study involved over 5000 hypertensive patients older than 70 years whose cognitive function was evaluated using the MMSE. Subjects were randomized to either candesartan or placebo, with the possibility of openly receiving other antihypertensive agents (excluding angiotensin-II receptor antagonists) to achieve adequate BP control. This caused 84% of the patients in the control group to receive treatment as well, whereas only 25% of the patients in the candesartan group took the drug as monotherapy, so it became very difficult to individualize the outcomes by treatment arm. This study did not shown improvement or aggravation of cognitive function. In our study, in which 98% of the patients were treated with lercanidipine and only 20% received additional therapy with an ACE inhibitor or doxazosin, a statistically significant improvement of cognitive function in the TMT scores after 6 months of treatment was observed. This finding is clinically relevant, not only because of improvement of cognitive function itself, but also because improvement has occurred after 6 months of treatment, whereas hypertension-related abnormalities that may lead to dementia are observed many years later. Lercanidipine is a highly lipophilic third-generation dihydropyridine calcium channel antagonist that is characterized by its vascular selectivity. The action of lercanidipine is much longer than other calcium channel antagonists, and its antihypertensive efficacy and tolerability have been documented in over 16 000 hypertensive patients. The favorable tolerability profile of this drug has been extensively documented in daily practice. The potential antiatherogenic effects of lercanidipine could explain the improvement of cognitive function especially of the vascular type. However, the role that BP reduction or the antiatherogenic effect of lercanidipine may play on cognitive function improvement is merely speculative and has not been investigated here. Lercanidipine is an alternative antihypertensive medication that can be seriously considered for the management of hypertensive patients with cognitive dysfunction, and it should be preferred to other dihydropyridine calcium channel antagonists that have been also shown to have beneficial effects on cognitive function.

In summary, lercanidipine was an efficient drug for achieving BP control in 68% of hypertensive patients who were previously uncontrolled or initiated antihypertensive pharmacological treatment. The safety profile of the drug was good, as shown by 98% of the patients still receiving lercanidipine treatment at the end of the study. Lercanidipine improved cognitive function after 6 months of treatment as measured using the MMSE. This improvement was even more remarkable in patients with adequate BP control, suggesting that better cognitive function may be associated with a reduction in BP.

Acknowledgments

We thank Marta Pulido, MD, for editing the manuscript and editorial assistance.

Disclosures

Dr Angel Navarro is Medical Director of Recordati España, the pharmaceutical company proprietary of the study drug lercanidipine.

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