Treatment of essential hypertension with calcium channel blockers: what is the place of lercanidipine?

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In all actual clinical guidelines, dihydropyridine calcium channel blockers (CCBs) belong to the recommended first line antihypertensive drugs to treat essential hypertension. Several recent large clinical trials have confirmed their efficacy not only in lowering blood pressure but also in reducing cardiovascular morbidity and mortality in hypertensive patients with a normal or high cardiovascular risk profile. In clinical trials such as ALLHAT, VALUE or ASCOT, an amlodipine-based therapy was at least as effective, when not slightly superior, in lowering blood pressure and sometimes more effective in preventing target organ damages than blood pressure lowering strategies based on the use of diuretics, beta-blockers and blockers of the renin-angiotensin system. One of the main clinical side effects of the first and second generation CCBs including amlodipine is the development of peripheral edema. The incidence of leg edema can be markedly reduced by combining the CCB with a blocker of the renin-angiotensin system. This strategy has now led to the development of several fixed-dose combinations of amlodipine and angiotensin II receptor antagonists. Another alternative to lower the incidence of edema is to use CCBs of the third generation such as lercanidipine. Indeed, although no major clinical trials have been conducted with this compound, clinical studies have shown that lercanidipine and amlodipine have a comparable antihypertensive efficacy but with significantly less peripheral edema in patients receiving lercanidipine. In some countries, lercanidipine is now available in a single-pill association with an ACE inhibitor thereby further improving its efficacy and tolerability profile.

Keywords: dihydropyridines, humans, hypertension, single-pill combinations

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1. Introduction

Among drugs currently available as first line treatments of essential hypertension, calcium channel blockers (CCBs) continue to receive a great deal of attention because of their well-recognized antihypertensive efficacy and their clear benefits in preventing cardiovascular complications and reducing cardiovascular mortality. Thus, in the past years, several large clinical trials such as ALLHAT, VALUE, ASCOT and ACCOMPLISH have confirmed the clinical interest of a CCB-based therapy for the management of normal and high cardiovascular risk hypertensive patients [1-4].

As a class, CCBs share the common feature of inhibiting cellular entry of calcium through voltage-dependent L and T-type calcium channels. Yet, there are significant differences between the various CCBs with regard to their binding sites and chemical structure. These differences account, in part, for some of the
Lercanidipine

Table 1. Vascular selectivity of lercanidipine in comparison with other calcium channel blockers.

| Drug            | IC$_{50}$ Vessels (nM) | IC$_{50}$ Heart (nM) | Ratio of selectivity |
|-----------------|------------------------|----------------------|----------------------|
| Lercanidipine   | 0.13                   | 12,000               | $1.1 \times 10^5$    |
| S-lercanidipine | 0.017                  | 1,700                | $1 \times 10^5$      |
| R-lercanidipine | 1.2                    | 4,800                | $2.5 \times 10^4$    |
| Nitrendipine    | 0.85                   | 18                   | $4.7 \times 10^2$    |
| Félodipine      | 0.23                   | 14                   | $1.6 \times 10^2$    |

IC$_{50}$: Concentration of the drug to inhibit 50% of the effect of 80 mM KCl in the rabbit.

observed clinical differences in dromotropy, negative inotropy and vascular selectivity observed between dihydropyridines (DHPs), verapamil and diltiazem [5].

Dihydropyridines are the most frequently prescribed CCBs in hypertension. Pharmacologically they can roughly be classified in three groups. The first generation consisted of short-acting DHP such as nifedipine, felodipine, nicardipine and isradipine. These CCBs were characterized by a short duration of action and the induction of a strong peripheral vasodilatation leading to the occurrence of flushes, reflex tachycardia and peripheral edema. Moreover, the use of these CCBs was associated with rapid and marked falls in blood pressure that could sometimes provoke acute cardiovascular complications including myocardial infarction. The second generation of DHP was developed with the idea to limit the acute vasodilatory effects and hence to prolong the duration of the blockade of calcium channels. This was achieved by developing slow-release forms of the same compounds (nifedipine GITS, felodipine SR, etc.) and with the development of long-acting CCBs such as amlopidine. With these compounds, side effects associated with the acute vasodilatation almost disappeared and the antihypertensive efficacy was prolonged over 24 h. The main side effect of this second generation CCB, however, was the development of peripheral edema owing to the sustained peripheral vasodilatation. The aim of the third generation of DHPs was to preserve the antihypertensive profile of the long-acting CCB while further reducing the incidence of peripheral edema. This was achieved with the development of new highly lipophilic compounds with strong membrane binding such as lacidipine, manidipine and lercanidipine. These new compounds are characterized by a long duration of action and an improved tolerability profile when compared with amlopidine as will be discussed here.

2. Pharmacological characteristics of lercanidipine

Lercanidipine is almost completely absorbed from the gastrointestinal tract and reaches its maximal plasma concentration after 1 – 3 h and is excreted in the urine. It is highly bound to proteins (> 98%) and has a distribution volume of 2 – 2.5 L/kg [7]. Lercanidipine is highly lipophilic; hence, the drug has a better penetration in hydrophobic cell membranes than other DHPs and penetrates even in smooth muscle cells surrounded by cholesterol-rich plaques [6]. This might explain its high efficiency in a wide range of patients, including patients with a high cardiovascular risk profile and diffuse atherosclerosis. As shown in Table 1, lercanidipine is highly selective for vessels when compared with first generation CCBs. The S-enantiomer of the compound has a higher affinity for L-type calcium channels than the R-enantiomer. In contrast to first generation CCBs, lercanidipine does not produce any reflex tachycardia and does not stimulate the sympathetic nervous system. The dose must be adapted in severe chronic renal failure (eGFR < 30 ml/min).

Another property of lercanidipine is a long duration of action, resulting in 24-h blood pressure control after a single dose despite a short plasma half-life (8 – 10 h because of a first pass effect in the liver). Once again, its lipophilic profile explains this apparent discrepancy, as lercanidipine is quickly stored in the hydrophobic component of the cell membrane layer. Lercanidipine induces a slow-onset, prolonged smooth muscle relaxation, resulting in peripheral and coronary vasodilatation and thus steady lowering of the blood pressure without important reflex tachycardia [8]. Lercanidipine is metabolized by CYP3A4; plasma concentrations are thus influenced by inducers or inhibitors of 3A4 such as cimetidine, ketoconazole and grape fruit juice. Several pharmacodynamic properties of lercanidipine have been investigated in vitro and in animal models of hypertension and these properties are summarized in Table 2.

3. Antihypertensive efficacy of lercanidipine in hypertension

Several studies have assessed the efficacy of lercanidipine as monotherapy in the treatment of hypertension [9-15]. Lercanidipine has been investigated at doses ranging between 5 and 40 mg/day. Significant dose-dependent reductions of
both systolic and diastolic blood pressures of 19 – 26 and 13 – 15 mmHg, respectively, have been reported with lercanidipine, and non-inferiority studies have demonstrated that lercanidipine is as effective in lowering blood pressure as amlodipine, the reference long-acting CCB. In all comparative studies lercanidipine was found to be at least as effective in lowering blood pressure as amlopidine but with a better tolerability profile as will be discussed later. Yet, whether lercanidipine provides as much cardiovascular protection in hypertensive patients as amlopidine remains unknown because no morbidity/mortality trial has been conducted with this third generation CCB. A detailed review of clinical studies conducted with lercanidipine has been published recently by Borghi et al. [16]. Lercanidipine has been studied in the elderly and in diabetic patients where it has been found to be also very effective [9,17]. It is also effective in cardiac ischemia [18,19]. This anti-ischemic effect was evaluated in a study including 23 patients with stable angina who performed bicycle exercise testing and simultaneous ambulatory radionuclide testing to estimate the left ventricular function, before and after the introduction of lercanidipine 10 – 20 mg. Lercanidipine increased in a dose dependent way the time to onset of ST segment depression and improved total exercise duration, this without changing heart rate with respect to the pretreatment level [19].

4. Lercanidipine: an improved tolerability profile

The main advantage of lercanidipine is that it induces less peripheral edema than other DHPs. Several studies were conducted to investigate this aspect and are summarized in Table 3. On average, peripheral edema develops in 0.6 – 9% of treated patients (at a dose of 10 mg), which is considerably lower than the 23% reported in the ASCOT trial [3]. Observational studies have shown that in patients previously treated with another DHP, switching from a first generation DHP to lercanidipine reduces the likelihood of developing peripheral edema by – 50% [20]. In observational studies this likelihood may be even lower. Thus, in an observational, prospective Phase IV study, the efficacy and tolerability of lercanidipine was investigated in private practices in Switzerland [13]. Lercanidipine was prescribed as monotherapy (n = 683), as step-on therapy (n = 844) or as a substitute for another drug (n = 672) to hypertensive patients (mean age 58 – 69 years; 10 – 22% diabetics); doses were up-titrated to 20 mg in case of insufficient blood pressure control after 4 weeks. Of the 182 patients that started lercanidipine because of peripheral edema with another calcium antagonist, only 10 experienced edema. Moreover, the persistence was very high at 98 – 99% and 63% reached the target blood pressure (≤ 140/90 mmHg) [13]. An even larger study including 9,059 Spanish patients (ELYPSE study) found similar results: the overall incidence of adverse events was 6.5%, of which 2.9% involved headache, 1.1% flushing, 0.6% palpitations and only 1.2% ankle edema [12].

The highest rate of peripheral edema (39.7%) was found in the TOLERANCE study [14]. This observational study included 650 hypertensive patients on lercanidipine or another DHP (amlodipine or nifedipine GITS) who were up-titrated from a low dose (10, 5 and 30 mg, respectively) to a high dose (20, 10 and 60 mg, respectively) of the mentioned drugs. Two explanations might account for the high rate of peripheral edema in this study. First, the peripheral edema was reported by the patient and might have been underestimated. Second, the dose of lercanidipine used was higher than in the other studies. Finally, the peripheral edema did not lead to drug interruption, as illustrated by high adherence rates (93.9 versus 93.7% in the amlopidine/nifedipine group). All these studies were observational, non-randomized ones, and thus selection bias cannot be excluded and the findings should be interpreted with caution. However, the only prospective, double-blind randomized trial, performed in stage I or II hypertensive elderly patients (≥ 60 years), also found significantly

| Table 2. Summary of pharmacodynamic properties of lercanidipine. |
|---|
| **Mechanism of action** |
| Selective blockade of L-type voltage-dependent calcium channels |
| Lowering of blood pressure by inducing a peripheral vasodilatation |
| High vascular selectivity |
| Little activity: no clinical relevant effects on heart rate or ECG parameters |
| Favorable effects on left ventricular hypertrophy |
| **Anti – atherogenic effects** |
| Dose-dependent in vitro inhibition of the proliferation and migration of arterial smooth muscle cells |
| Anti-oxidant effect in hypertensive patients with or without type 2 diabetes |
| Decrease of atherosclerotic lesions in the hypercholesterolemic rabbit |
| **Renal effects** |
| Dilation of the afferent and efferent arterioles in the SHR rat |
| Inhibition of glomerular hypertrophy in the SHR rat |
| Decrease of albuminuria in the SHR rat and in diabetic patients |
| **Metabolic effects** |
| No impact on the lipid profile and glycemia |
| **Others** |
| Reduced the occurrence of stroke in the SHR rat |
| Reduced the incidence of peripheral edema |
Lercanidipine

more edema in the amlodipine group than in the lercanidipine or lacidipine groups (COHORT) [11]. Two other studies conducted in both men and women demonstrated by using an objective evaluation method (the so-called water displacement technique) that lercanidipine produced statistically significant less ankle edema than nifedipine GITS 30 mg and amlodipine 10 mg [21,22].

Why lercanidipine leads to less leg edema remains unknown. It is generally believed that DHP induces an increase in the intra-capillary hydrostatic pressure owing to arteriolar vasodilatation, and that reflex sympathetic activation avoids adequate post-capillary venous vasodilatation. As mentioned earlier, lercanidipine induces less sympathetic activation and this may lead to less peripheral edema [23]. Although a single-blind cross-over study in 22 male hypertensive patients confirmed the difference in edema-forming potential as measured by the water displacement method, this study did not find a difference in interference with postural vasoconstrictor mechanisms between amlodipine (10 mg) and lercanidipine (20 mg) [24].

Thanks to its slow onset of action, reflex tachycardia is rare with lercanidipine, and this is also true for flushing and acute hypotension. This was illustrated by an analysis of 14 placebo-controlled, double-blind trials including 1,850 patients: 2.1% of patients presented tachycardia, 1.7% palpitations and 2.0% flushing [25].

5. The future: a single-pill combination of lercanidipine and enalapril

The use of single-pill drug combination has gained an increased popularity in the management of hypertension. The most important rationale for using single-pill combinations is to improve efficacy and tolerability [26]. Improvement in efficacy in terms of a reduction in blood pressure over single-agent therapy has been shown for most combinations. In a recent review, Quan et al. [27] outlined the clinical evidence for the association of an angiotensin receptor antagonist and hydrochlorothiazide and that of a CCB and an ACE inhibitor, both of which have demonstrated benefits particularly in specific patient populations. Interestingly, as shown by Stergiou et al., some associations of therapeutic principles may be more effective than others [28]. Thus, combining drugs acting on a similar system may be less effective than associating drugs with different mechanisms of action. In the recently published ACCOMPLISH trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) > 75% of patients receiving a fixed dose combination achieved the blood pressure target of < 140/90 mmHg at 6 months and this irrespective of the single-pill combination used (CCB/ACE inhibitor or ACE inhibitor/diuretic) [4]. The increased efficacy of fixed dose combinations may be particularly relevant for the management of patients with a high cardiovascular risk such as patients with severe hypertension. For these patients, the ability to reach the target blood pressure faster may be a very important issue with regards to the results of the VALUE trial that demonstrated a significantly reduced incidence of cardiovascular events in the amlodipine-treated versus the valsartan-treated group during the first 6 months owing to better blood pressure control [2]. The use of combinations should increase the likelihood of reducing blood pressure whatever the

Table 3. Large trials that evaluated the tolerability and efficacy of lercanidipine therapy in daily clinical practice.

| Study (year)                  | n     | Type                  | Medication                                   | Duration | Peripheral edema (%) |
|------------------------------|-------|-----------------------|----------------------------------------------|----------|----------------------|
| ELLE Study (Elderly, 2003)   | 324   | Randomized            | Lercanidipine 10 – 20 mg                      | 24 weeks | 2.8                  |
|                              |       |                       | Lacidipine 2 – 4 mg                           |          | 7.5                  |
|                              |       |                       | Nifedipine GITS 30 – 60 mg                    |          | 10.1                 |
| LEAD study (Adults, 2003)    | 250   | Randomized            | Lercanidipine 10 – 20 mg                      | 8 weeks  | 5.5                  |
|                              |       |                       | Felodipine 10 – 20 mg                         |          | 13                   |
|                              |       |                       | Nifedipine GITS 30 – 60 mg                    |          | 6.6                  |
| LAURA study, 2006 [15]       | 3,175 | Open-label, non-comparative | Lercanidipine 10 – 20 mg/day                 | 6 months | 5.1                  |
| TOLERANCE study, 2008 [14]   | 650   | Observational         | Lercanidipine 20 mg versus amlodipine 10 mg or nifedipine GITS 60 mg | 2 months | 39.7                 |
|                              |       |                       |                                             |          | 57.3                 |
| Burnier, 2007 [13]           | 2,199 | Observational, non-interventional | Lercanidipine 10/20 mg; monotherapy or substitution therapy | 2 months | 0.6 – 3              |
| ELYPSE, 2002 [12]            | 9,059 | Observational         | Lercanidipine 10 mg                          | 3 months | 1.2                  |
| COHORT, 2002 [11]            | 828   | Prospective, randomized, double-blind | Lercanidipine 10 – 20 mg versus amlodipine 5 – 10 mg versus lacidipine 2 – 4 mg | 12 months | 9                    |
|                              |       |                       |                                             |          | 19                   |

984 Expert Opin. Drug Metab. Toxicol. (2009) 5(9)
gender, sex and race of the patient. Single-pill combinations also have important advantages over single agents in terms of tolerability profile as the side effects of one drug can be counterbalanced by the effects of another. For example, when CCBs are combined with blockers of the renin-angiotensin system, there is lower incidence of peripheral edema [29]. Finally, the prescription of single drug combination improves drug adherence [26].

The recent results of the ACCOMPLISH trial have demonstrated a certain advantage of the CCB/ACE inhibitor association over the ACE inhibitor/diuretic combination in the management of high cardiovascular risk, mainly in obese and hypertensive patients [4]. These results have now provided new incentives for the use and development of drugs combining a CCB and a blocker of the renin-angiotensin system. This strategy is further encouraged by the observation that most patients need at least two drugs to achieve good blood pressure control.

Several randomized studies have been conducted to investigate the combination of lercanidipine and an ACE inhibitor to be given once a day in patients with mild-to-moderate hypertension generally poorly controlled with a monotherapy of either the ACE inhibitor or lercanidipine Table 4. In these groups of patients, a larger percentage of patients achieved the target blood pressures using the single-pill combination. The fixed-dose formulations of lercanidipine 10 mg/enalapril 10 or 20mg are now approved in several European countries for the treatment of hypertension, and a 12-week, randomized, double-blind trial showed effective blood pressure lowering and high tolerability of this combination, with < 1.5% of patients developing peripheral edema [32]. Yet, because of the use of enalapril in the combination, the incidence of cough was ~ 4 – 5%. The use of this single-pill combination may be of particular interest for the management of patients with difficult-to-control blood pressures and hypertensive patients with kidney diseases because of the renal protective effects of the ACE inhibitor [35]. Owing to the efficacy of CCB and ACE inhibitors in patients with coronary heart disease, this single-pill combination might be attractive for this indication but clinical studies should be performed to demonstrate the clinical benefits of using this association.

6. Conclusion

Together with blockers of the renin-angiotensin system, CCBs belong to the three chief classes of antihypertensive drugs. The development of a third generation of calcium antagonists with a preserved long-term antihypertensive efficacy and a better tolerability profile should be considered as an important improvement within the class. In some aspects, the added clinical value of the new calcium antagonists can

| Study          | Patient (n) | Hypertensive patient category | Type of study            | Treatment                                                                 | Duration | Mean blood pressure difference (mmHg) | Remarks                                      |
|---------------|-------------|-------------------------------|--------------------------|---------------------------------------------------------------------------|----------|--------------------------------------|----------------------------------------------|
| Agrawal, 2006 [32] | 174         | Diabetes type 1 or 2 (aged 18 – 80 years) | Randomized double-blind  | Enalapril 20 mg + lercanidipine add-on versus enalapril 20 mg + hydrochlorothiazide add-on | 20 weeks | -9.3 versus -7.4                     |                                               |
| Cleophas, 2001 [30] | 34          | Diabetes type 2               | Open-label               | ACE inhibitor + lercanidipine versus ACE inhibitor + metoprolol Sequential treatments | 6 months | -6 ± 10                              | Blood pressure reduction to the point of withdrawal of β blocker |
| Grandi, 2008 [31] | 24          | Never treated hypertension   | Randomized pilot study   | Ramipril + candesartan versus Ramipril + lercanidipine                    | 6 months | -13.3 versus -12.3                   | Less ventricular remodeling in lercanidipine group |
| Puig, 2007 [34]  | 75          | Elderly (aged 60 – 85 years)  | Randomized double-blind  | Lercanidipine 10 mg versus enalapril 20 mg versus combination of the two versus placebo in crossover sequence | 4 weeks per treatment | -5.0 versus -5.9 versus -16.9 as compared to placebo |                                               |
be compared to the development of angiotensin II receptor blockers that also offer an improved tolerability profile for an equal efficacy when compared to ACE inhibitors. Unfortunately, the development of the newer CCB suffers from a paucity of clinical studies in hypertensive patients with various comorbidities that probably limit their wider use in clinical practice. Lercanidipine belongs to this third generation of calcium antagonists. It has a proven antihypertensive efficacy in mono- and combination therapy and its main advantage over first and second generation DHPS is its lower incidence of adverse effects, in particular peripheral edema. This side effect occurs even less frequently when lercanidipine is combined with enalapril. In view of the recent results of the ACCOMPLISH trial, lercanidipine prescribed alone or in combination with enalapril could represent an interesting therapeutic alternative for the management of hypertensive patients with a high cardiovascular risk profile.

7. Expert opinion

On the basis of the actual role of DHP CCBs in the management of hypertensive patients, lercanidipine has an interesting potential of development because it provides as much blood pressure control as amlodipine but with a better tolerability profile. Thus, lercanidipine is a real alternative to be used in patients well controlled with a CCB but developing peripheral edema. However, now that amlodipine has become a generic drug, the price issue might be a limiting factor for a wider use of lercanidipine. The development of a single-pill combination with enalapril is a very important step as single-pill associations containing CCBs and blockers of the renin-angiotensin system are becoming increasingly popular because of their efficacy. However, one might regret that in the proposed associations only one dose of lercanidipine is included (10 mg) and that the company has chosen to associate lercanidipine with an ACE inhibitor, which alone produces cough in up to 10% of patients, rather than with an angiotensin II receptor blocker, which has a placebo-like tolerability profile.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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