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Letter to Editor

All About Fixed-Dose Combination Lercanidipine/Enalapril: Ten Questions and Answers

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Introduction

Despite different antihypertensive drugs are available, blood pressure (BP) control is sub-optimal in many countries [1,2]. Calcium channel blockers (CCBs), particularly dihydropyridine-CCBs, (DHP-CCBs), are the first–line drugs in antihypertensive therapy and are recommended by International Guidelines [3,4], either as monotherapy, or in combination with renin-angiotensin aldosterone system (RAAS) inhibitors, to achieve blood pressure (BP) control.

Lercanidipine, a third-generation dihydropyridine-CCBs, is characterized by high vascular selectivity, high lipophilic properties, slow onset and long duration of action [5], therefore it is different from a number of other calcium antagonists [6]. Enalapril is a long-acting ACE inhibitor [7] which reduces plasma levels of angiotensin II, decreasing peripheral vascular resistance. Therefore enalapril and lercanidipine have a synergic effect.

1. What are the most important pharmacological properties of Lercanidipine/Enalapril

Lercanidipine reversibly inhibits the voltage-activated L-type Ca2+ channels in smooth muscle cells of arteries, leading to peripheral vasodilatation and, therefore, to blood pressure (BP) reduction [8,9].

Differently from other DHP-CCBs, (particularly amlodipine and lacidipine), lercanidipine inhibits both L and T calcium channels [10]. There is evidence that T channels are particularly expressed in the efferent renal arterioles [11], while L channels are particularly located in the afferent arterioles [12,13]. Therefore lercanidipine, blocking both L and T channels, dilates renal arterioles and prevents the increase of glomerular pressure. This effect leads to the reduction of filtration fraction and, therefore, avoids the progression of kidney disease [14,15].

Enalapril is a prodrug, which is hydrolyzed in the liver to the active metabolite, enalaprilat. Enalaprilat lowers plasma levels of angiotensin II and, consequently, decreases peripheral vascular resistance and BP values [7,16]. Moreover, enalapril counteracting the action of angiotensin II on both afferent and efferent renal arterioles, has a synergic effect with lercanidipine on kidney vessels.

It is worth to mention that enalaprilat has a plasma half-life of 11 hours, therefore the antihypertensive effect of enalapril is between 24–36 hours [16].

2. What is the evidence of Lercanidipine/Enalapril antihypertensive efficacy?

The antihypertensive efficacy of Lercanidipine/Enalapril (10-20 or 20-20 mg/once daily) has been evaluated in several double-blind, randomized, comparative trials, in large observational studies and summarized in numerous reviews. In patients with low-moderate hypertension, Lercanidipine/Enalapril combination, significantly reduces SBP and DBP, assessed either as office BP, home BP or 24-hours BP monitoring. This effect is associated with high rate (45.0%–69.6%) of responder patients (SBP/ DBP decrease >20 mmHg/ 10 mmHg) or subjects with normal BP values [17,18]. The therapeutic efficacy of the combination has also been demonstrated in elderly [19], in diabetic patients [20] and in obese subjects [21,22].

The antihypertensive activity of Lercanidipine/Enalapril is also evident in patients with stage 2 hypertension. The FELT

study [23] has shown a statistical significant reduction of BP with 10/20 mg (p=0.003) and 20/20 mg (p<0.001)/daily, compared with placebo. The responder and normalization rates of BP values were achieved in 61% and 75% of patients respectively.

3. What about the duration of Lercanidipine/Enalapril antihypertensive effect?

Lercanidipine/Enalapril, once/daily, decreases BP values during 24 h, with a significant reduction of morning BP rise. This effect is mainly caused by the long duration of lercanidipine pharmacological effect and by the long half-life of enalaprilat (11 hours). A large number of studies have demonstrated the sustained antihypertensive effect of Lercanidipine/Enalapril, assessed with 24 hours BP monitoring [23-27].

4. Is the antihypertensive effect of Lercanidipine/Enalapril different according to the age and gender of patients?

Lercanidipine/Enalapril combination significantly decreases BP independently of age and gender [25, 28].

5. What is the relationship between Lercanidipine/Enalapril and endothelial dysfunction?

Hypertension is associated with impaired endothelium-mediated nitric oxide (NO) bioavailability, increased oxidative stress, low-grade inflammation, vasoconstriction and high peripheral vascular resistance [29]. In patients with essential hypertension, lercanidipine significantly enhances endothelium-mediated vasodilation, through the release of NO and the reduction of oxidative stress, assessed by the low plasma level of lipoperoxides, isoprostanes, malondialdeyde and asymmetric dimethylarginine [30,31]. Moreover, a beneficial effects of ACE inhibitors, enalapril included, has been reported in essential hypertensive patients with endothelial dysfunction [32,33,34]. Therefore, both lercanidipine and enalapril have a synergic effect in improving the endothelial function.

6. What is the effect of Lercanidipine/Enalapril on Augmentation Index and Central Aortic SBP?

In hypertensive patients with isolated systolic hypertension lercanidipine, significantly reduces the Augmentation index, as well the aortic SBP and pulse pressure, proving an improvement of arterial stiffness [35, 36]. Similar effect has been observed with enalapril in patients with mild essential hypertension [37]. Therefore, enalapril enhances the activity of lercanidipine in decreasing the markers of arterial stiffness, such as the Augmentation index, central aortic SBP and pulse pressure. This evidence translates in a protective effect in hypertensive patients, reducing the risk of cardiovascular events [38,39,40].

7. What about the effect of Lercanidipine/Enalapril on sympathetic system?

Differently from felodipine and nifedipine, chronic administration of lercanidipine, does not induce sympathetic activation [41, 42]. Moreover enalapril, differently from amlodipine, decreases muscle sympathetic-nerve activity in patients with chronic renal failure [43].

Lercanidipine/Enalapril, differently from other antihypertensive combinations, such as amlodipine-enalapril and hydrochlorothiazide-enalapril, significantly decreases muscle sympathetic activity [26]. Similar finding has also been reported in obese hypertensive patients, comparing Lercanidipine/Enalapril with felodipine-enalapril [44]. The reduction of sympathetic nerve activity is associated with low level of plasma norepinephrine, a marker of sympathetic overactivity [41,42]. This aspect has an important clinical relevance, considering that, in hypertensive patients; sympathetic overdrive is associated with tachycardia and development of cardiovascular events.

8. What is the evidence of Lercanidipine/Enalapril on renal protection?

Hypertension remain a major risk factor for kidney disease and blood pressure control is the main mechanism for preventing the progression of chronic renal failure. Lercanidipine and enalapril, in addition to the antihypertensive effect, have a complementary pharmacological activity on the kidney vessels. Indeed, lercanidipine blocks both L and T channels, while enalapril inhibits the vasoconstriction induced by angiotensin II. Therefore, both drugs dilate the afferent and efferent renal arterioles and reduce intraglomerular pressure. Some studies have reported that lercanidipine decreases proteinuria in patients with type 2 diabetes [45] and in subjects with atherosclerotic renal artery stenosis [46]. Moreover, the RAAS blocking drugs provide a higher antiproteinuric effect, independently of arterial pressure reduction [47]. The improvement of renal function with Lercanidipine/Enalapril has been demonstrated in patients with chronic renal failure. The ZAFRA study [48] has shown an improvement in renal function, assessed through the creatinine clearance increase and the RED LEVEL trial [49], performed in hypertensive patients with albuminuria, has reported a significant reduction of albuminuria only with Lercanidipine/Enalapril combination, and not with enalapril-amlodipine combination. Globally proteinuria was decreased by 33-37% with the combination Lercanidipine/Enalapril RAAS blocking drugs [50]. The PAIT- Survey Follow-Up [51], performed in patients with hypertension, diabetes and proteinuria has shown that the prevalence of subjects with microalbuminuria was significantly (p<0.01) decreased after 6 months of Lercanidipine/Enalapril treatment. Particularly this effect has been much greater with Lercanidipine/Enalapril (- 41.3%) compared with amlodipine-valsartan (-15.6%), amlodipine-perindopril (-11.8%) and verapamil-trandolapril, (-19.2%). Moreover, the proportion of patients which reversed from albuminuria to normoalbuminuria was significantly higher (p < 0.01) with Lercanidipine/Enalapril, compared with the other treatments (28.6% vs 14.8%, 10.7% and 17.8% respectively).

The improvement of renal function obtained with Lercanidipine/Enalapril, differently from enalapril-amlodipine combination, is associated with a significant (p<0.05) reduction of renal arterial resistance index, showing that the combination improves the renal vascular hemodynamics (26).Therefore, among different combinations of CCBs with inhibitors of RAAS, Lercanidipine/Enalapril can be considered the best association to control albuminuria in patients with hypertension and albuminuria, because the single components have a complementary pharmacological effect on kidney function.

9. What are the pleiotropic effects of Lercanidipine/Enalapril?

Lercanidipine improving endothelial function [30,31] and increasing NO bioavailability, shows a vascular atheroprotective effects. NO decreases oxidative stress, reduces vascular intimal and smooth muscle cell proliferation, decreases the plasma levels of E-selectin, P-selectin, adhesion molecules, inhibits cholesterol accumulation, LDL oxidation and platelet aggregation to the endothelium. Through these effects, lercanidipine decreases the risk of atherothrombotic

events [52,53]. The antagonists of RAAS inhibitors play an important role in decreasing vascular inflammation, oxidative stress, smooth muscle cell proliferation and vascular remodeling and are involved in cardiovascular protection [54,55]. Therefore, enalapril enhances the cardioprotective effect of lercanidipine.

10. What about the Lercanidipine/Enalapril tolerability?

Treatment with Lercanidipine/Enalapril combination is well tolerated, with a low incidence of adverse events. The most common side effects, treatment-related, are flushes, palpitations, tachycardia, dizziness and dry cough, generally of mild severity [20, 22,26,27, 56]. Particularly, peripheral edema, the most frequent adverse event of CCBs [57] occurs in a very small percentage of patients, [22, 23,26,28,48], because the addition of enalapril to lercanidipine reduces the post-capillary pressure, avoiding fluid extravasation [58]. This finding has a clinical relevance because it avoids the risk of treatment withdrawal and increases the adherence of patients to the antihypertensive therapy [59].

Conflicts of interest:

Gokhan Faikoglu and Kubra Saygisever-Faikoglu are employees of Recordati

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