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Use of Lercanidipine and Enalapril in Combination Therapy for the Treatment of Hypertensive Patient

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Abstract

Due to its increased risk of heart failure, myocardial infarction, and stroke, hypertension is a significant risk factor for premature death. Antihypertensive medications can lower cardiovascular (CV) morbidity and death. To achieve blood pressure (BP) goals, the majority of hypertensive individuals require more than one antihypertensive medication. Only 20% to 40% of people respond well to monotherapy when trying to lower their blood pressure. The pathophysiology of hypertension is mediated by a number of factors, such as elevated peripheral vascular resistance, elevated cardiac effort, and hypervolemia. Multiple mechanisms can be targeted for increased BP reduction. Because the underlying mechanism causing the BP increase is either different or was previously treated with the lower dose, increasing the dose of a single medication frequently does not have the desired BP-lowering effect. In addition, medications that target various pathways may work to reduce blood pressure. The renin-angiotensin-aldosterone system is known to be enhanced by the effects of diuretics and to become active as a response to the decreased circulating blood volume. The renin-angiotensin-aldosterone system is elevated, therefore by combining a diuretic with a renin-angiotensin aldosterone system blocker; blood pressure may be reduced more successfully. If possible side effects of a drug's are vary on dosage, maximum dose may also be effective to reduced B P. Renin-angiotensin-aldosterone system blockers can be added to calcium channel blockers (CCBs) by vein dilation to decrease the occurrence of peripheral oedema that is associated with higher dosages of CCBs. This combination is a potential therapy for the management of hypertension due to the efficiency of enalapril and lercanidipine in lowering blood pressure, the safety profile, and the usage of CCBs and ACE inhibitors together in clinical studies with excellent CV hard end point outcomes.

Keywords: ACE inhibitors • Calcium channel blockers • Lercanidipine • Enalapril • Hypertension

Introduction

There are several different hypertensive phenotypes caused by blood pressure (BP) regulation mechanisms include cardiac output, peripheral vascular resistance, and circulating blood volume. Choosing the best medication for each patient is often a crucial undertaking because each mechanism may increase BP in a hypertensive patient to a different level. To keep an appropriate blood flow to the tissues, cardiac output regulation is crucial. A larger stroke volume or a higher heart rate is the two factors that contribute to increased cardiac output in hypertension. Reduced arterial pressure and increased cardiac output are both effects of lower total peripheral resistance. The kidneys hold onto water and salt until the tissue blood flow and blood pressure return to normal. This retention happens when tissue blood flow is below normal. The autonomous and central nervous systems also have influence over these physiological processes. Increased peripheral vascular resistance seems to be the main hemodynamic anomaly connected to high blood pressure. Through a variety of physiological mechanisms, peripheral vascular resistance influences the flow of blood to the organs. These include the sympathetic nervous system's role in the vessels, the impact of circulating or local vasoactive hormones like angiotensin II (AT-II), epinephrine, and norepinephrine, antidiuretic hormone, atrial natriuretic peptide, and endothelin, and the actions of endothelial Due to the intricacy of the mechanisms underlying hypertension, different people will respond differently to antihypertensive therapy, necessitating the individualization of treatment.

The development of targeted antihypertensive medication was made possible by taking into account the various BP processes. The first vasodilator was hydralazine, which was then followed by calcium channel blockers (CCBs) on vascular smooth muscle cells, blockade of post-synaptic alpha-adrenoceptors on peripheral sympathetic neurons (alpha blockers), and finally vasodilation accomplished by blockade of the renin-angiotensin-aldosterone system (RAAS) (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], direct renin inhibitors [DRIs]). The BP responses were varied when these compounds were given to a heterogeneous population. When both renal arteries are severely stenotic or when only one kidney is functional, ACE inhibitor therapy may result in rapid renal impairment. Symptoms of hypotension are frequently seen in ACE-induced acute renal failure, although they disappear after the medication is stopped. BP reductions with an ACE inhibitor may be modest in patients with low renin hypertension, such as hypertension in the elderly and in people of African descent, where the RAAS is typically inhibited. The average BP responses to single drugs were 9.1 mmHg for systolic and 5.5 mmHg for diastolic BP at a normal dose, according to a meta-analysis of 354 randomised double-blind placebo-controlled studies of monotherapy. Therefore, especially for patients close to the normal thresholds, a meaningful BP response is rarely achieved with medication alone. After the patient has received monotherapy, what should be done if the BP has not decreased to the desired level? Should we start combination medications at low doses or double the dose of monotherapy?

In comparison to higher dose monotherapy, combination therapy increases BP control rates and takes less time to reach goal BP with equal or better tolerability. According to a meta-analysis of more than 40 research, combining two antihypertensive medications from different classes results in a substantially greater reduction in blood pressure than raising the dosage of a single medication. Cost savings and improved compliance could be further gains. Figure 1 depicts possible medication combinations, including beta blockers and diuretics, ARBs and diuretics, ACE inhibitors and diuretics, CCBs and ACE inhibitors, CCBs and diuretics, and thiazides combined with potassium-sparing diuretics (Figure 1).

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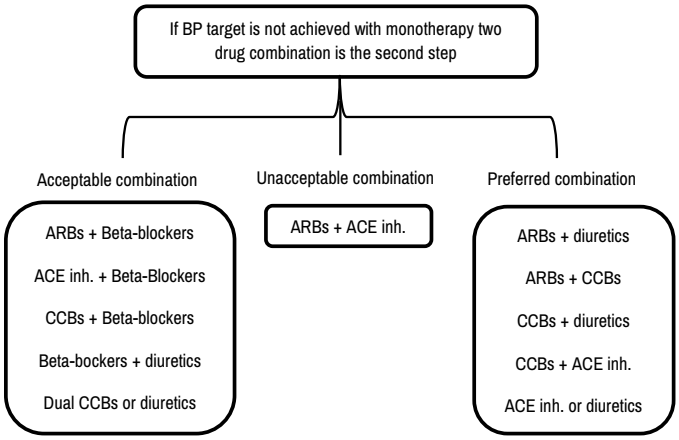

Abbreviation: ACE inh: Angiotensin- converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; BP: Blood pressure; CCBs: Calcium channel blockers.

Figure 1. Combination of drug for hypertension control.

In clinical studies, different combinations of two antihypertensive medications or combinations of two medications plus a placebo were evaluated for their efficacy in lowering blood pressure and in preventing cardiovascular (CV) hard end points like CV deaths and patient hospitalisation for myocardial infarction, stroke, and heart failure. The LIFE trial randomly assigned hypertension patients to either losartan or atenolol as their first line of treatment. To reach BP objectives, hydrochlorothiazide was added. After a 5-year follow-up, the losartan-based group had a 13% lower composite primary CV end point than the atenolol-based group. The secondary stroke end point, which was decreased by 25% in the losartan-based group, was where the greatest benefit could be shown. Patients with hypertension were randomly assigned to receive either valsartan or amlodipine in the VALUE study. To help BP achieve its objective, hydrochlorothiazide was added to each group. Both treatment groups used equivalent additional medications. A 4.2-year follow-up was the average. Compared to the valsartan group, the BP was decreased more quickly and efficiently in the amlodipine-based treatment group. The amlodipine-based therapy group experienced fewer myocardial infarctions and strokes than the valsartan-based group. Hypertensives above the age of 80 who were also hypertensive in the HYVET study were given either the diuretic indapamide or a placebo. If additional ACE inhibitor perindopril or a placebo pill was required to reach the desired blood pressure, it was given. In comparison to placebo, the drug combination of indapamide and perindopril significantly reduced the incidence of heart failure (64%) and stroke (30%). In the HOPE study, patients who had previously experienced a myocardial infarction who were given ramipril experienced lower blood pressure and a lower incidence of cardiovascular events than those in the placebo group. 25 In the FEVER trial, individuals with BP 160/90 mmHg who had previously received antihypertensive medication were treated with the calcium antagonist felodipine in comparison to a placebo. The incidence of all CV end points was statistically significantly lower in the felodipine group [1-5].

Mechanism of action according to the pharmacology: Pharmacokinetics of combination of lercanidipine with enalapril

A chiral carbon atom is found at position 4 of the 1,4-dihydropyridine ring in lercanidipine, a dihydropyridine CCB of third generation. Almost insoluble in water, lercanidipine hydrochloride is a microcrystalline, citrine powder. Inhibiting calcium entry through L-type calcium channels in smooth muscle cells of the CV system causes peripheral vasodilatation, which has the antihypertensive effect. In contrast to other dihydropyridines, it is a highly lipophilic medication with a slower onset and longer duration of action. The large percentage of L-type calcium channels in arteries also contributes to its strong vasoselectivity. Lercanidipine has a low incidence of side effects, is well tolerated, does not trigger reflex tachycardia or sympathetic activation, and has a renoprotective effect. Lercanidipine has a short plasma half-life of 3 hours and a long duration of action, making it a once-daily medicine according to pharmacokinetics. Given that it is quickly absorbed from the digestive tract and has a 10% absolute bioavailability in fed patients, it should be administered prior to meals. Cytochrome P450 3A4 is responsible for the metabolism of lercanidipine, which is similarly eliminated in the urine and faeces. The antihypertensive effects of lercanidipine are effective at doses up to 20 mg, and these doses are well tolerated. In patients with advanced renal (glomerular filtration rate 10 mL/min or on dialysis) or hepatic impairment, the medication is not advised. Enalapril maleate, also known as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]], is the maleate salt of the drug enalapril. -l-alanyl] -l-proline, salt of (Z)-2-butenedioate (1:1). The powder form of enalapril maleate is white to off-white. It is dispersible in ethanol, methanol, and water. Enalapril is an oral prodrug that is metabolised to the active metabolite, enalaprilat, which has antihypertensive properties and can lower plasma levels of AT-II by preventing the final stage of its activation. Enalapril reaches its highest serum concentrations after oral dosing in about an hour. After 4-6 hours, the various enalaprilat concentrations are reached. The plasma half-life of enalaprilat is approximately 11 hours, compared to the short 1.3 hour half-life of enalapril. Elderly patients may be more susceptible to side effects if the dose is increased. A low dose of enalapril (1.25-5 mg) provided the same level of blood pressure control and renoprotection in individuals with advanced renal failure (mean GFR =15 mL/min) while having fewer side effects. The sympathetic nervous system and the RAAS may be reflexively activated by dihydropyridine CCBs. In addition, edoema is a side effect of the vasodilatory effects of the CCBs and may be linked to arteriolar dilation, which increases intracapillary pressure. The side effects of peripheral vasodilatation, such as leg edoema, swelling, flushes, headaches, and palpitations, were much less common with high doses of lercanidipine than with high doses of amlodine or nifedipine. A dihydropyridine CCB that also contains an ACE inhibitor or an ARB greatly lessens vasodilatory edoema, primarily due to reduced capillary pressure caused by veining dilatation. When an ACE inhibitor is used with CCBs, this action may amplify the antihypertensive effects of ACE inhibition since CCBs may encourage a negative sodium balance and a rise in AT-II levels [6-10].

Safety & efficacy

The advantages of the fixed combination of lercanidipine and enalapril have been proven in numerous trials. Patients with hypertension, the elderly, and diabetics have all been studied to determine the effectiveness of lercanidipine and enalapril. 75 patients between the ages of 60 and 85 were randomly assigned. The four treatments; lercanidipine 10 mg, enalapril 20 mg, lercanidipine 10 mg + enalapril 20 mg (lercanidipine/enalapril), and placebo were given to each patient in turn over the course of four weeks. In senior patients, the lercanidipine/enalapril combination treatment was well tolerated and exhibited additive antihypertensive effects on both ambulatory and office BP. A multicenter, double-blind, randomised trial included patients with diabetes and mild-to-moderate hypertension. Nonresponders were randomly assigned to add-on medication with either lercanidipine 10 mg or hydrochlorothiazide 12.5 mg after a 4-week course of enalapril 20 mg followed by a 2-week run-in with a placebo. At the conclusion of the trial, hydrochlorothiazide and lercanidipine each reduced systolic blood pressure by 9.6 mmHg and 6 mmHg, while diastolic blood pressure declined by a mean of 9.3 mmHg and 7.4 mmHg, respectively. In an observational trial with 315 patients, the equivalent decreases in systolic and diastolic blood pressure were 11.4% and 11.3%, respectively, after initiating lercanidipine/enalapril. Age, sex, and diastolic blood pressure all decreased, but neither did systolic blood pressure. After a mean of 2.88 months of treatment with lercanidipine/enalapril, the BP control rates considerably increased from 10.2% at baseline to 51%. Last but not least, just one patient experienced negative symptoms, which included a chronic dry cough.

Fixed dose consumption of enalapril and lercanidipine

Apolipoprotein A, which is a large, hydrophilic glycoprotein linked to a low-density lipoprotein particle known as lipoprotein(a), also known as Lp(a), potentiates thrombosis by preventing the attachment of plasminogen-binding proteins to the surface of endothelial cells. Lp(a) may serve as a sign of tissue or vascular damage. The soluble receptor of advanced glycation end products (sRAGE) is a molecule found on the cell surface of immunoglobulins and serves as a receptor for AGEs, which have been linked

to endothelial dysfunction, arterial stiffening, and hypertension. AGEs have a proinflammatory effect. Inhibiting the impact of AGE-mediated processes, sRAGE has AGE-binding capabilities. According to reports, patients with carotid and femoral atherosclerosis and those with higher plasma levels of sRAGE have decreased rates of coronary atherosclerosis. The aetiology of vascular injury is influenced by soluble CD40 ligand, which has been identified as a molecular link between angiogenesis, thrombosis, and inflammation. Finally, by directly consuming nitric oxide (NO) and producing reactive oxygen species, serum myeloperoxidase (MPO) lowers nitric oxide (NO) bioavailability, impairing endothelium-dependent dilatation while increasing tetrahydrobiopterin bioactivity and NO generation. In a randomised, double-blind clinical experiment, the effects of the drug combination lercanidipine/enalapril on the endothelial damage biomarkers LP(a), sRAGE, soluble CD40, and MPO were investigated. As anticipated, the combination of lercanidipine and enalapril reduced blood pressure more effectively than the monotherapies. In the same trial, CCBs and ACE inhibitors both had unfavourable effects on lipid and glucose metabolism, however lercanidipine/enalapril was more effective than either drug alone at improving Lp(a). The combination of lercanidipine and enalapril had a better effect than either drug used alone, increasing sRAGE levels while lowering those of soluble CD40 and MPO. These findings did not depend on blood pressure, indicating that lowering blood pressure with lercanidipine and enalapril had a more noticeable lowering effect on endothelial damage, which improved levels of LP(a), sRAGE, soluble CD40, and MPO.

It has also been demonstrated that patients with type II diabetes and stage 1 hypertension respond favourably to the lercanidipine/enalapril combination. Enalapril 10 mg or equivalent dosages of other ACE inhibitors (perindopril 4 mg in 6 cases and Quinapril 20 mg in 3 cases) were administered to patients with a resting diastolic blood pressure more than 90 mmHg for three months, followed by three months of lercanidipine 10 mg. When the diastolic blood pressure was still greater than 90 mmHg after 6 weeks of combination therapy, the doses of Metoprolol or lercanidipine were increased to 200 mg and 20 mg, respectively. The mean arterial pressure decreased by 6 mmHg after 3 months on lercanidipine, indicating that lercanidipine combined with ACE is more efficient than metoprolol. The combination of lercanidipine and enalapril was found to increase cellular expression of the glucose transporter type 4 in comparison to lercanidipine and hydrochlorothiazide. Human lymphomonocytes ability to activate insulin signalling may play a significant role in diabetes patients, suggesting that CCB-based medication combinations are more advantageous in obese or diabetic patients due to their effects on insulin sensitivity. In a study that investigated the impact of combination therapy with an ACE inhibitor + CCB or thiazide diuretic on these measures, arterial stiffness and augmentation index were examined in hypertensive individuals with metabolic syndrome. When lercanidipine and enalapril are combined, the reduction in pulse wave velocity is comparable to that of hydrochlorothiazide, but there is a greater decrease in the augmentation index, suggesting a possible additive role for the combination in the augmentation of central blood pressure. This combination may provide effective protection against target organ damage, such as left ventricular hypertrophy and peripheral vascular damage. In a research using lercanidipine/enalapril or thiazide diuretic, non-invasive assessments of wall-to-lumen ratio and other morphological features of retinal arterioles were examined using scanning laser Doppler flowmetry. Patients received treatment for a full year. Pulse wave velocity and central blood pressure were also assessed while capillaroscopy was used to assess capillary density. During therapy with lercanidipine alone, the structure of the retinal arteries significantly improved, and this improvement persisted after treatment with lercanidipine and enalapril. However, after treatment with lercanidipine and hydrochlorothiazide, the improvement stopped being seen.

Discussion

There have been numerous studies that compare the medication adherence of various pharmacological groups. The persistence of antihypertensive medication was the subject of one investigation. Patients with mild to severe hypertension were randomised to receive monotherapy with either ACE inhibitors, AT-II blockers, CCBs, beta blockers, or diuretics, and they were monitored for 24 months after starting the treatment. In contrast to 51.6% for beta blockers (44.8%) and 34.4% for diuretics, the persistence of treatment was highest for ACE inhibitors (64.5%) and AT-II blockers (68.5%). The appearance of side effects was the leading cause of treatment cessation. ARBs and ACE inhibitors are widely known for their manageable side effects. CCBs exhibit slightly lower rates of persistence. Patients were more likely to stick with the lercanidipine treatment than other dihydropyridines (59.3% vs. 46.6%) when comparing patients treated with dihydropyridine CCBs. Unfortunately, there isn't any concrete evidence about how well the combination of lercanidipine and enalapril is tolerated, how much it costs to treat patients, or how it stacks up against other therapy regimens. An observational study that included >8,000 patients, general practitioners, and internal medicine specialists found that the fixed combination of lercanidipine and enalapril was effective, with 94% of participants rating it as "very good" or "good" in terms of its effectiveness. The doctors also rated 97% of patients' adherence as "very good" or "good" and 97% of patients' tolerability as "very excellent" or "good." Generally speaking, the once-daily administration of a fixed-dose combination of lercanidipine and enalapril, either 10 mg/10 mg or 10 mg/20 mg, seems to enhance blood pressure control in individuals who are not responding to monotherapy and to have a favourable tolerability profile. Only a significant proportion of patients reported stopping their treatment because of major side effects [10-15].

Conclusion

This review's goal was to assess the effectiveness, safety, and tolerability of using lercanidipine and enalapril together. Excellent BP control rates with side effects equivalent to monotherapy are the key benefit of lercanidipine/enalapril combination therapy. There are no doubt those patients, especially the elderly, use a lot of medicines every day, not just for hypertension but also for other common ailments that affect the aged, like coronary artery disease, type II diabetes, dyslipidemia, depression and sleeping difficulties, pain relief, etc. Patient annoyance and low adherence rates may be the results of this. By lowering the number of tablets required daily, fixed-dose combination medications may address these problems and improve adherence and assimilation into daily routines. The selection of a fixed-dose combination may also improve patient adherence to therapy if it is linked to a decreased incidence of side effects. Clinical trials comparing the combination of ACE and CCBs to beta blockers and diuretics reveal positive results for CV morbidity and mortality, but further research is needed to determine whether these results were caused by a particular medicine or class. According to this viewpoint, randomised clinical trials comparing various ACE/CCB combinations to one another and evaluating strict CV end points are required. Comparing ARB- and ACE-based combinations for their impact on hypertension and cardiovascular protection is another significant open question that has to be explored.

Acknowledgement

None.

Conflict of Interest

None.

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