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Lercanidipine Over Other Calcium Channel Blocker in Elderly Patients & its Renal Protection in Future

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Abstract

A calcium channel blocker called lercanidipine shows promise as a treatment for hypertension, especially in older people. Exhibiting greater effectiveness in comparison to other calcium channel blockers, it presents encouraging opportunities for the management of hypertension. Its use has a low risk to renal function, which sets it apart from other medicines in its class that might have a negative impact on the kidneys. Consequently, lercanidipine distinguishes itself as a beneficial and well-tolerated treatment choice for hypertension patients, providing a possible way to address cardiovascular issues without jeopardizing renal function, particularly in the elderly population.

Keywords: Lercanidipine; Hypertension; Calcium channel blocker; Renal Protection

Abbreviations: eGR: estimated Glomerular Rate; CS: Cerebral Stroke; CAD: Coronary Artery Disease; LVOTO: Left Ventricular Outflow Tract Obstruction; RAA: Renin-Angiotensin Axis.

Introduction

Hypertension is the most prevalent chronic illness observed in primary care and one of the major risk factors for cardiovascular (CV) death and morbidity [1]. Data from extensive clinical trials using randomization and meta-analyses [2] have demonstrated the advantages of lowering high blood pressure (BP) to avoid harm to target organs and death in geriatric people [3]. Reduce the risk of CV events by 5 mmHg for 10 mmHg for systolic blood pressure (SBP) or diastolic blood pressure (DBP) and the reduction is greater when a medication combination regimen is used [4]. Regretfully, several cross-sectional studies have found insufficient management of hypertension [5]. Based on the findings of published research, this work attempts to give a critical assessment on the effects of lercanidipine on blood pressure, metabolism, and cardiovascular health in the management of hypertension, with an emphasis on the most current data [6].

Lercanidipine- Characterization of Drug

One 1,4-DHP L- and T-type CCB is lercanidipine [7]. It works by blocking the uptake of calcium into smooth and vascular muscle cells. This results in vasodilation and muscular relaxation, which lowers blood pressure and peripheral vascular resistance. Lercanidipine has a long-lasting impact and strong vascular selectivity since it belongs to the third generation of DHP-CCBs [8]. Lercanidipine comes in two distinct enantiomers, (S)-lercanidipine and (R)-lercanidipine, since it has two ester groups in the DHP ring at

positions 3 and 5. The (S)-enantiomer is the more powerful one, according to studies [9].

Lercanidipines high lipophilicity, which results from the drugs phenyl alkylamine side chain at the DHP ring's third position and ensures the drugs molecule, has easier penetration to its destination as well as a higher concentration in phospholipid membranes, is one of its most important features [10].

Pharmacology of Lercanidipine

Following oral administration, the medication undergoes prolonged first-pass hepatic metabolism and is mostly absorbed from the gastrointestinal system. Since lercanidipine is better absorbed when food is present [11], Lercanidipine binds to plasma proteins in the bloodstream extensively-more than 98% [12]. Like other DHP-CCBs, lercanidipine is metabolized in the liver by the cytochrome P450 (CYP) isoform CYP3A4. It is noteworthy to mention that CYP is involved in the metabolism of up to 30% of all prescription medications. Thus, frequent concurrent use of lercanidipine and other medications may result in unfavourable drug interactions [13].

The findings show that groups of patients with cirrhosis or mild to severe renal impairment, or the elderly, seldom see any change in the pharmacokinetic profile of lercanidipine. As a result, there is no need to change the lercanidipine dosage given to these individuals. To prevent achieving excessive plasma concentrations, the dose must be lowered in cases of severe renal impairment when the estimated glomerular rate (eGFR) is less than 30 ml/min/m^2 [14].

Lercanidipines' plasma half-life is rather brief, lasting about 8 to 10 hours. This, however, is not consistent with the drug's real action, which is noticeably longer. Because of its high lipophilicity, lercanidipine may be stored in the hydrophobic portion of the cell, accounting for both its slow beginning of action and long-lasting antihypertensive impact. As a result, lercanidipine permits 24-hour blood pressure regulation and can be given once daily [15].

Mechanism of Action

Lercanidipine's capacity to reversibly block high-voltage dependent L-type calcium channels, which are found in cardiac tissue, skeletal muscle, and all excitable cells, may be its most significant mode of action. By relaxing the arterial smooth muscles and promoting both peripheral and coronary vasodilation, the blockage of these channels within the cardiovascular system (CVS) enables a decrease in peripheral vascular resistance [16].

Thus, lercanidipine has anti-ischemic and antihypertensive properties. Surprisingly, because lercanidipine takes time to take effect, its reduction of blood pressure is not accompanied with undesirable reflex tachycardia or other negative symptoms of sympathetic activation [17]. Moreover, T-type low-voltage calcium channels, which are found in a number of organs including the kidneys and heart and are a significant molecular target, can be inhibited by lercanidipine. Research has demonstrated that CCBs that block both L- and T-type calcium channels, such lercanidipine, enhance renal health by lowering proteinuria and glomerular hypertension and by generally improving glomerular morphology [18].

It has been demonstrated that lercanidipine has advantageous anti-atherogenic properties. Preclinical research has shown that it inhibits the proliferation and migration of arterial smooth muscle cells in addition to reducing atherosclerotic plaques in hypercholesterolemic rabbits [19]. Furthermore, several research have shown that lercanidipine could have a role in end- organ protection. Research indicates that the medication lessens hypertrophy of the left ventricle [20]. Furthermore, preclinical evidence suggests that lercanidipine treatment lowers the risk of cerebral stroke (CS) [21].

Indication for Administration

Hypertension is the main lercanidipine indication. Numerous studies have demonstrated the effectiveness of lercanidipine as a mono therapy for the treatment of hypertension. It has been determined that people with mild to severe hypertension can lower their blood pressure by taking lercanidipine once day at a dosage of 5 to 20 mg [22]. In individuals with severe essential hypertension, treatment with lercanidipine at a dosage of 20-40 mg per day effectively lowers blood pressure, according to a non-blind research. Additionally, an unreported trial demonstrated that lercanidipine, administered at a dosage of 10-30 mg daily, was an efficacious therapy for resistant hypertension that did not respond to other medication classes [23]. Furthermore, isolated systolic hypertension and mild to severe essential hypertension in older people can be effectively treated with lercanidipine [24].

Nonetheless, multi therapy was found to be more advantageous, and the 2018 guidelines from the European Society of Hypertension/European Society of Cardiology advise treating a hypertensive patient with a combination of two medications. Therefore, a renin- angiotensin system blocker plus a CCB or diuretic should often be the first line of therapy. Patients with diabetes, coronary artery disease (CAD), and cerebrovascular disease benefit most

from the combination of CCBs, such as lercanidipine (recommendations of grade IA) [25]. Additionally, research has demonstrated that lercanidipine in combination with any kind of medication reduces blood pressure more significantly than lercanidipine used alone [26].

Absorption

When used orally, lercanidipine is a medication that is gradually absorbed from the digestive system. Within 1.5-3 hours, the plasma's maximum drug concentration (Cmax) is attained [27,28]. During the initial hepatic flow, lercanidipine undergoes significant metabolism, resulting in an absolute bioavailability of 10% in the fed patient [29]. Since the presence of a high-fat meal or the inclusion of surfactants increases the absolute oral bioavailability of lercanidipine, it is best to take it prior to meals. In one study, d-tocopheryl polyethylene glycol 1000 succinate (TPGS) was added to lercanidipine–hydroxypropyl methyl cellulose (HPMC) nanoparticles. It was shown that this combination had an oral bioavailability that was 2.47 times greater than the raw material alone [30].

Adverse Effects

The potential negative effects (AEs) of lercanidipine are compiled in this review. Vasodilation during the initial phases of treatment has been linked to the prevention of adverse events in patients receiving lercanidipine [23]. Fourteen double-blind, placebo-controlled clinical studies have been conducted to examine the safety and incidence of adverse events (AEs) associated with lercanidipine. Across all research, 1850 individuals with stable angina pectoris (SAP) or hypertension took part. The majority of the randomized patients received lercanidipine at dosages ranging from 10 to 20 mg for a maximum of 129 days [31].

After receiving lercanidipine, 26.8% of patients experienced side effects. Headache (5.6%), edema (2.4%), tachycardia (2.1%), flushing (2.0%), palpitations (1.7%), rhinitis (1.3%) and hypokalaemia (1.2%) were the most frequently reported adverse responses. Conversely, 20.3% of responders were placebo-treated patients, and headache (3.8%), hypokalaemia (1.3%) and hyperuricemia (1.1%) were the most often reported adverse events. Most patients had mild or severe adverse events (AEs); nevertheless, the majority of them were deemed unconnected to lercanidipine. A group of 104 hypertensive individuals with an ischemic stroke were also included in a randomized, open-label, controlled research that demonstrated a minimal risk of adverse events following lercanidipine usage. Facial flushing (n = 3; 5.7%) was one of the reported adverse events, while ankle edema (n = 2; 3.8%), was the other documented adverse response [32]. 3175 patients receiving lercanidipine for six months made up the research population in another multi centre, prospective, non-comparative, open-label trial. Patients were categorized into four categories based on their cardiovascular risk: low, medium, high, and extremely high. The presenting of this medication's adverse effects was one of the study's goals. 11.5% of the trial participants experienced adverse effects following lercanidipine treatment, with edema (5.1%) being the most frequent, followed by headache (3.3%), flushing (2.5%), and asthenia (1%). There were no appreciable differences in the occurrence of adverse events by cardiovascular risk category [33].

Contraindications

A patient with a creatinine clearance of less than 10 milliliters per minute (hepatic or renal insufficiency) should not get lercanidipine medication. Additionally, women who are pregnant, nursing, or who are not using an effective form of contraception should not use lercanidipine. It is not recommended to use lercanidipine in the following clinical conditions: unstable angina pectoris, untreated congestive heart failure, left ventricular outflow tract obstruction (LVOTO), and within one month of a myocardial infarction [34]. It is also not recommended to use lercanidipine with CsA or potent CYP3A4 inhibitors. Combining lercanidipine with CsA, an immunosuppressive medication, raises the blood serum concentration of CsA, which may be linked to a number of adverse consequences. When adding lercanidipine to a patient's therapy, elderly patients or those with mild to severe renal or hepatic impairment should be handled very carefully. Additionally, it is not advised for anybody under the age of 18 to use lercanidipine [35].

Interactions

CYP, especially the CYP3A4 isoform, is responsible for the metabolism of lercanidipine. The liver and intestines are the primary sites of drug metabolism for the CYP3A4 isoform. With 30% of all CYP content in the human liver, CYP3A4 is the most prevalent P450. In addition, it is present in the brain, colon, small intestine, prostate, and breast [36]. An example of a strong CYP3A4 inhibitor is ketoconazole. Since this enzyme is known to metabolize lercanidipine, we may anticipate that if the two medications interact, lercanidipine's plasma concentrations may change. According to studies, taking both drugs together boosted lercanidipine's Cmax by eight times and its area under the curve (AUC) by almost fifteen times. Although cyclosporine, also known as cyclosporin A or CsA, is a commonly used immunosuppressive medication in transplantology, there is a significant chance that it will interfere with other medications. Concomitant usage of CsA (CYP3A4 substrate and inhibitor) resulted in a three-fold increase in lercanidipine bioavailability and a

two-fold rise in ciclosporin plasma levels. Because of the potential for adverse effects, it's critical to keep an eye on CsA concentrations in patients using lercanidipine and CsA concurrently [37].

Certain CYP3A4 inhibitors, such grapefruit juice, will also increase the oral bioavailability of lercanidipine. When these two medications are taken together, the antihypertensive impact will be greater than when lercanidipine 10 mg is used alone [24]. For CYP3A4, metoprolol is a frequent substrate, and for CYP2D6, midazolam. Research has indicated that the co- administration of midazolam with lercanidipine or metoprolol and lercanidipine does not result in any notable pharmacokinetic interactions. The administration of lercanidipine did not influence the bioavailability of either midazolam or metoprolol; nevertheless, dosage modification could be required. Combining lercanidipine with β-methyldigoxin at dosages of 10-20 mg did not result in any clinically significant interactions either. Nevertheless, patients who use these medications together should be closely monitored because digoxin toxicity is a possibility [38].

One CYP3A4 enzyme inhibitor is cimetidine; however, when cimetidine and lercanidipine were given together, there was no discernible change in the drug's primary pharmacokinetic characteristics or plasma concentration. Because of this, when medications are taken concurrently, there is no need to change the dosage. Within the class of drugs known as statins, simvastatin is first an inactive prodrug that is metabolized mostly by CYP3A4 into an active molecule called beta-hydroxy acid. In a particular investigation, the simultaneous administration of 20 mg of lercanidipine and 40 mg of simvastatin led to a 56% rise in the drug's bioavailability and a 28% increase in its active β-hydroxy acid metabolite.

There was no alteration in lercanidipine's bioavailability. An additional investigation revealed interplay between lercanidipine and haloperidol, an antipsychotic, resulting in hypotension. This interaction was most likely caused by haloperidol, an isoenzyme inhibitor that inhibits the metabolism of lercanidipine (CYP 3A4). Hypotension may result when using lercanidipine and fluoxetine concurrently. Competition for binding with the CYP3A4 isoenzyme, which metabolizes fluoxetine and lercanidipine and raises AE and lercanidipine plasma concentrations, may be the cause of this interaction. The mechanism of interaction between fluoxetine and lercanidipine is shared by sertraline and paroxetine, although the interactions' side effects are distinct. Whereas the combination of sertraline and lercanidipine resulted in myalgia and polyuria, the combination of paroxetine and lercanidipine induced polyuria and elevated transaminase levels [39].

Comparing Lercanidipine as a Hypertensive Medication to Other Anti- Hypertensive Drugs

Efficacy of Lercanidipine: According to clinical studies, lercanidipine is a medication that effectively treats hypertension in both newly diagnosed patients and those whose prior treatments did not work. It is also well-tolerated in these populations. In a Burnier, et al. trial, individuals who were moved to lercanidipine because their blood pressure was either poorly managed or they had adverse events (AEs) following prior medication demonstrated similar drops in blood pressure to those who had never received treatment for hypertension. Comparable findings were seen in the ELYPSE investigation. Moreover, just 6.5% of individuals said they had any adverse events during the trial [40].

Patients with metabolic syndrome and the elderly can both safely utilize lercanidipine. In the Viviani research, individuals with diabetes who took lercanidipine saw considerable drops in the blood glucose, fructosamine, and glycated hemoglobin A1 (HbA1) in addition to a significant drop in blood pressure. Furthermore, lercanidipine did not trigger sympathetic activation and was successful in lowering ischemia-related signs and symptoms in individuals with stable angina in the Acanfora, et al. research. The LAURA research discovered that lercanidipine improved blood pressure more in patients with higher cardiovascular risk without significantly affecting tolerability [41].

Lercanidipine in Comparison to Other DHP-CCBs: Research has found discrepancies in the effects of two subclasses of calcium antagonists: DHP CCBs (lercanidipine included) and non-DHP CCBs, taking into account the degree and mechanism of nephroprotection. Non-DHPs can even suppress the rise in urine protein levels, slow down the formation of mesangial matrix, and prevent glomerular scarring, according to preclinical research [42]. Non-DHP CCBs significantly reduce proteinuria levels and had comparable effects on the hypotensive impact, according to a meta-analysis evaluating the effects of the subclasses on blood pressure parameters and proteinuria levels in patients with arterial hypertension [43].

Comparison of Lercanidipine with Other DHP-CCBs: The two primary mechanisms by which hypotensive medications preserve the kidneys are blood pressure reduction and intra-renal processes. Based on statistical research, lercanidipine's antihypertensive impact does not exhibit a significant difference from that of other DHP-CCBs. On the intracellular

level, lercanidipine, a novel class of DHP-CCBs, exhibits a greater capacity for nephron protection than older DHP-CCBs. According to analyses assessing the potential for negative responses in in both new and traditional DHP-CCB therapies, lercanidipine use is linked to a decrease in the frequency and exacerbation of AE, primarily peripheral edema , and as a result, a decrease in the risk of DE challenging as a result of this AE . The use of lipophilic calcium antagonists reduces the incidence of edemas by 57%, according the investigation conducted by Makani, et al [44].

A notably reduced frequency of adverse events (AEs) following lercanidipine than following other CCBs has also been seen in previous trials [45]. Antonio Cherubini, et al. Elderly and Lercanidipine (ELLE) research [46] has demonstrated that lercanidipine, as opposed to lacidipine and nifedipine, has the best antihypertensive impact. Lecanidipine is the most efficient and secure medication of the three, as evidenced by the fact that it had the lowest rate of adverse drug reactions (ADRs). Furthermore, the incidence of these adverse drug reactions (ADRs) was discovered to be much lower in the lercanidipine group in the TOLERANCE study designed by Barrios, et al.

The study's main variable was the compatibility of high lercanidipine dosages with high nifedipine and amlodipine doses. For individuals in need of high dosages of medicine, lercanidipine administration appears to be a suitable alternative. The study by Leonetti, et al. found that lercanidipine had shown an identical antihypertensive impact with a tolerance profile comparable to or better than that of lacidipine and amlodipine, making it a viable choice for older hypertensive patients.. The study compared the tolerability of long-term treatment with lercanidipine versus other CCBs in hypertensive patients. Furthermore, although earlier research has indicated that the class of CCBs may be involved in stroke prevention Cheng, et al. retrospective 6-year study found that lercanidipine was substantially more successful than nifedipine in lowering the risk of stroke [45].

Comparison of Lercanidipine with Other Antihypertensive Drugs: The well-known class of drugs known as angiotensin-converting enzyme inhibitors, or ACE-I, is also frequently used to treat nephropathies, hypertension, and congestive heart failure. Derosa, et al.'s study [46] evaluated the effects of enalapril and lercanidipine in monotherapy to those of the two medications in a fixed combination and discovered that the combination of the two medications was more successful in lowering blood pressure than the individual monotherapies. Similar findings were seen in other research, such those of Mancia, et al [47]. But when evaluating the effectiveness of the two monotherapies, lercanidipine by itself appeared to lower blood pressure more significantly than perindopril [48].

Inhibiting the renin-angiotensin-aldosterone system (RAAS), angiotensin II type 1 receptor antagonists (ARBs) and ACE-I share similar mechanisms of action and are often used in the treatment of hypertension. The recommendations of the European Society of Hypertension/European Society of Cardiology (ESH/ESC) recommend multi therapy as a means of treating hypertension, are compatible with these findings. Because of their complimentary modes of action, CCBs (such lercanidipine) and RAAS inhibitors work well together in a multi therapy regimen to lower blood pressure. Furthermore, it has been claimed that lercanidipine plus an ACE-I or ARB combination lowers glucose and lipid levels [49].

The general health of individuals receiving multi therapy as a treatment for hypertension might benefit greatly from this approach. According to a research, compared to hydrochlorothiazide and enalapril multi therapy, lercanidipine and enalapril multi therapy dramatically decreased the augmentation index. This implies that the combination may contribute to the preservation of the cardiovascular system. Furthermore, compared to enalapril plus amlodipine and enalapril plus hydrochlorothiazide, a research indicated that the combination of lercanidipine and enalapril reduced hypertension-related target organ damage and improved kidney functions the best [50]. The RED LEVEL trial indicated that although there was no significant difference in blood pressure management between the two groups, the combination of enalapril and lercanidipine had a better anti-albuminuric effect than enalapril and amlodipine. Similar findings were reported in a research that indicated multitherapy of lercanidipine with enalapril had the greatest rate of albuminuria decrease among treatments with various combinations of CCBs and RAAS blockers. This data may support the use of RAAS inhibitors in conjunction with lercanidipine to lower blood pressure and albuminuria rates in diabetic individuals who have hypertension [51].

Antihypertensive Activity in Elderly Patients: The effectiveness of lercanidipine as an antihypertensive medication in older adults with mild-to-moderate hypertension has been assessed in three multicenter, double-blind randomized trials, in addition to other research and questionnaires [52]. Lercanidipine was compared to lacidipine and amlodipine in the COHORT research including hypertension individuals with a 69–70 year old mean age. Following six months, there was no significant difference in the BP reductions observed with lercanidipine (-29.6/-14.5 mmHg), amlodipine, and lacidipine. Comparable outcomes were seen for the responder rate as well (about 50% at lower doses and up to 80% after increasing the dosage). Lercanidipine and nifedipine GITS were more effective than lacidipine in lowering DBP in the Elderly and Lercanidipine study,

which had patients with a mean age of 73 years. However, there was no difference in the efficacy on SBP. The AGATE trial looked into lercanidipine's ability to lower blood pressure in people who were older.

A comprehensive study conducted in general practice has supported this conclusion, showing a similar drop in SBP/DBP (-24/14 mmHg vs. -29/13 mmHg) and a similar rate of BP normalization (65% and 60%) among patients who are ≥65 or older. Furthermore, similar decreases in blood pressure (SBP/DBP -26/-14 mmHg and -24/-14 mmHg) and blood pressure normalization rate (66% and 61%) were found in the male and female participants of this survey. In all, 72% of individuals responded to a 10 mg dosage, whereas 29% required a 20 mg dose to achieve blood pressure management [53].

As a result, lercanidipine's therapeutic effect is independent of age or gender. Given that:

1. Most hypertensive patients are older than 65;
2. It is more difficult for elderly women than for elderly men to achieve blood pressure control;
3. According to international guidelines, CCBs are appropriate medications for treating hypertension in the elderly; this finding has significant therapeutic implications [54].

Nephroprotective Effect of Lercanidipine: As a member of a novel class of CCBs, lercanidipine demonstrates pleiotropic properties that aren't brought about by the agents' class effect but rather by other attributes. They reduce the progressive damage to the kidneys by having a good impact on renal parameters in addition to influencing the lowering of blood pressure [55]. Lercanidipine was shown to widen both afferent and efferent arterioles in the kidneys, lowering or maintaining intra glomerular pressure in preclinical experiments on hypertensive rats. The process was linked to the blocking of T-type and L-type calcium channels, which is common in most calcium channel blockers. Although they can also be found in afferent arterioles, T-type calcium channels are mostly found in efferent arterioles [40,92]. It has been demonstrated that simultaneous L and T channel blocking improves renal viability and reduces proteinuria in individuals with chronic kidney disease (CKD). Because both L-type and T-type calcium channels are simultaneously affected, there is a decrease in glomerular filtration fraction as well as blood pressure. This causes the new generation of medications to have nephroprotective effects that are comparable to those of medications that block the renin-angiotensin axis (RAA) [56].

Through inhibition of cell proliferation and therefore prevention of lumen narrowing, lercanidipine reduced thickening of the walls of tiny arteries and arterioles, especially renal ones, as well as vascular neointima,, in preclinical trials. Additionally, it decreased tubulointerstitial fibrosis and tissue inflammation, which are linked to the maintenance of renal function, as well as decreased albuminuria in double-transgenic rats [57].

Preclinical and clinical investigations have demonstrated the antioxidant properties of lercanidipine. By blocking the primary intracellular source of free radicals, xanthine oxidase (XO), cyclooxygenase (COX), and NADPH oxidase (NOX), it reduces the amount of free radicals produced. Furthermore, it lowers markers of oxidative stress, including endogenous nitric oxide synthase (NOS) inhibitors, leukocyte-derived vascular NO oxidase, Myeloperoxidase (MPO), metalloproteinase-9 (MMP-9), malondialdehyde (MDA), asymmetric dimethylarginine (ADMA), plasma lipoperoxidase, and isoprostanes (IsoPs). It also prevented cholesterol buildup by lowering the amounts of reactive oxygen species within cells [58].

Lecanidipine increases NO bioavailability in blood vessels and glomeruli while inhibiting NO oxidase and lowering NOS inhibitor immunoreactivity. This, combined with its anti- inflammatory properties, may be the cause of a decrease in monocyte infiltration, extracellular matrix formation, and renal vessel fibrosis [59]. It has been noted that an increase in mesangial cells might cause alterations in mesangial matrix proteins, both in terms of quantity and quality, and disrupt the transit of macromolecules throughout the mesangium, so exacerbating the progression of glomerular sclerosis. By inhibiting activator protein-1 (AP-1) and the cell cycle transition from the G1 to the S phase, lercanidipine counteracts these processes by limiting the proliferation of mesangial cells. Additionally, it affects the transcription of genes that stimulate mesangial cells to produce platelet-derived growth factors (PDGFs), such as granulocyte/monocyte colony-stimulating factor and interleukin-1 beta (IL-1β) [60].

The studies show that lercanidipine increases NO concentration, most likely as a result of decreased cellular calcium concentration, and decreases the activation of intracellular protein kinases, specifically protein kinase C (PKC) isoforms, as well as the ADMA-metabolizing enzyme dimethylarginine dimethylaminohydrolase. Lower PKC activity was also linked to lower albumin permeability by endothelial cells. It has been demonstrated that lercanidipine lowers blood levels of lipoprotein A, C-reactive protein, E-selectin, and P-selectin in patients. A decrease in the expression of intercellular adhesion molecules (ICAMs) implicated in vascular and tissue injury was seen in both experimental and subsequent clinical trials. Furthermore, lercanidipine was shown to up regulate fibronectin expression, which aids in the healing of injured tissues [61].

The vasoconstrictive effects of norepinephrine are further improved by a new family of CCBs, such as lercanidipine, which has been demonstrated to decrease norepinephrine secretion and block the renal action of endothelin. The chemicals mentioned above had a diminished impact on renal vasoconstriction, which prevented additional endothelial dysfunction. The table below provides an overview of the most important lercanidipine nephroprotective mechanisms.

Mechanism of Kidney Protection	Exerted Influence
Influence affecting both L type and T type calcium channel	Reduction in BP while maintaining constant intra glomerular pressure
Suppression of cell proliferation in renal arterioles	Prevention of thickening of the vesicular middle membrane and vesicular neointima prevention of lumen narrowing
Reduction in tissue inflammation and tubule interstitial fibrosis	Decrease in albuminuria preservation of renal function
Inhibition of free radical producing enzymes	Exerting antioxidant effect
Decrease in oxidative stress marker	Exerting antioxidant effect
Increases in NO bioavailability in blood vessels and glomeruli	Reduction in monocyte infiltration extracellular matrix formation and fibrosis in renal vessel
Inhibition of cholesterol accumulation	Anti- atherosclerotic effect
Inhibition of AP1 and the cell cycle transition from G1 to S phase of mesangial cell	Inhibition of mesangial cell proliferation
Modulation of transcription of IL1 beta and granulocytes monocytes called stimulating factor genes in mesangial cells	Inhibition of mesangial cell proliferation
Reduction in PKC activity	Decreases in permeability of albumin by glomerular endothelial cells
Decreases in expression of intracellular adhesion molecule	Reduction in blood vessels and tissue damage
Increase in fibronectin expression	Restoration of damage tissue

Table 1: over view of the most important lercanidipine nephroprotective mechanisms.

The Future: A Single-Pill Combination of Lercanidipine and Enalapril

The therapy of hypertension has seen a rise in the usage of single-pill medication combinations. The improvement of tolerance and efficacy is the primary justification for the use of single-pill combinations. For the majority of combinations, effectiveness has been demonstrated to be improved over single-agent treatment in terms of lowering blood pressure. Quan, et al. recently reviewed the clinical data supporting the combination of hydrochlorothiazide and an angiotensin receptor antagonist, as well as the combination of a CCB and an ACE inhibitor. Both treatments have shown promise, especially for distinct patient categories. As a result, pairing medications with distinct mechanisms of action may be more beneficial than combining medications working on the same system. Regardless of the single-pill combination used (ACE inhibitor/diuretic or CCB/ACE inhibitor), > 75% of patients receiving a fixed dose combination at six months achieved the blood pressure target of < 140/90 mmHg in the recently published ACCOMPLISH trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) [62].

Fixed dosage combinations have demonstrated enhanced effectiveness, which may be especially important when managing patients at high cardiovascular risk, such as those with severe hypertension. Regarding the results of the VALUE trial, which showed a significantly lower incidence of cardiovascular events in the amlodipine-treated group compared to the valsartan- treated group during the first six months due to better blood pressure control, the ability to reach the target blood pressure faster may be a very important issue for these patients. Regardless of the patient's gender, sex, or ethnicity, the usage of combinations should boost the chance of lowering blood pressure. In terms of tolerability profile, single-pill combinations can provide significant advantages over single medicines since the adverse effects of one medication can be offset by the benefits of another. Peripheral edema, for instance, is less common when CCBs and renin-angiotensin system blockers are used together. Lastly, medication adherence is improved when a single medication combination is prescribed [63].

The therapy of high cardiovascular risk, particularly in patients who are obese and hypertensive, may benefit from the CCB/ACE inhibitor combination over the ACE inhibitor/diuretic combination, according to the latest results of the ACCOMPLISH study. These findings have created new motivation for the usage and research of medications that combine a CCB with a renin-angiotensin system blocker. The fact that the majority of patients require at least two medications to attain adequate blood pressure management supports this technique even more [64].

Several European countries have approved the fixed-dose formulations of lercanidipine 10 mg/enalapril 10 or 20 mg for the purpose of managing hypertension. A 12-week, double-blind trial demonstrated the combination's high tolerability and effective blood pressure lowering, with less than 5% of patients experiencing peripheral edema. However, due to the combination of enalapril, the incidence of cough was around 4–5%. Because of the ACE inhibitor's renal protective properties, the use of this single pill combination may be especially interesting for the management of patients with blood pressure that is difficult to regulate and hypertensive patients who have kidney disorders [65].

Conclusion

Elderly people may find lercanidipine to be an especially useful and promising calcium channel blocker for hypertension. Because of its higher efficacy compared to other medications in its class, it is positioned as a viable treatment choice. The renal safety profile of lercanidipine sets it apart from other calcium channel blockers, which is an important factor that makes it an appealing option for those who want to control their hypertension without sacrificing their kidney function. The results highlight its effectiveness and favourable side effect profile, underscoring its potential importance in treating cardiovascular issues in the aging population.

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