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The fourth-generation Calcium channel blocker: Cilnidipine

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A B S T R A C T

Several classes of antihypertensive agents have been in clinical use, including diuretics, α -blockers, β -blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARB), and organic calcium channel blockers (CCBs). All these drugs are being currently used in the treatment of Hypertension & various disease conditions of the heart either alone or in combination. Cilnidipine is a new antihypertensive drug distinguished from other L-type Ca^{2+} channel blockers or even other antihypertensives, which will be useful for selection of antihypertensive drugs according to the pathophysiological condition of a patient.

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1. Hypertension or high blood pressure

Hypertension is one of the most important risk factors for cardiovascular diseases, including ischemic and haemorrhagic stroke, dementia, ischemic heart disease, heart failure, vision loss, and kidney failure. Hypertension is a multifactorial and multifaceted disease in which elevated blood pressure is only one sign of multiple underlying physiological abnormalities.^{1–3}

Hypertension or high blood pressure is a leading cause of death. The condition is often called a “silent killer” because its symptoms can go undetected until damage to the body has occurred. Because of this, it is one of the most significantly under-diagnosed and under-treated medical conditions all over the world. High blood pressure is usually a lifelong condition. High blood pressure can occur at any age but is particularly prevalent in people with a family history of high blood pressure, people who are overweight or obese, people with diabetes, and heavy drinkers.^{4,5}

2. Antihypertensive drugs

Several classes of antihypertensive agents have been in clinical use, including diuretics, α -blockers, β -blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARB), and organic calcium channel blockers (CCBs). All these drugs are being currently used in the treatment of hypertension and various disease conditions of the heart either alone or in combination. They have specific indications, therapeutic efficacies and limitations for the treatment of an individual patient. A patient has to consume these medicines for lifetime accommodating and adjusting to all their side effects.⁶

Clinically, an important goal of antihypertensive therapy is to prevent the occurrence of cardiovascular complications. It has been suggested that increased sympathetic activity is the common link among many of the “non pressure-related” coronary risk factors in hypertension. More importantly hyperactivity of sympathetic nervous system often triggers hypertensive complications including ischemic heart disease,

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strokes, heart failure, and renal failure which show the importance of controlling sympathetic nerve activity in clinical practice. Sympathetic nerve activity is one of the major culprits implicated in the onset of hypertension. Julius⁷ reported that the occurrence of a hyperkinetic state, that is, one in which both cardiac output and heart rate are elevated, was five times more frequently observed in patients with borderline hypertension than in the normotensive population.

3. Calcium channel blockers (CCBs)

Calcium channel blockers (CCBs), comprising two subclasses – dihydropyridines and non-dihydropyridines – have been for many years one of the mainstays of hypertension therapy. Calcium channel blockers (CCBs) share a common mechanism of action. However, the manner in which they exert their pharmacological effects is different between subclasses. Dihydropyridine (DHP) CCBs tend to be more potent vasodilators than non-dihydropyridine (non-DHP) agents, whereas the latter have more marked negative inotropic effects. Both subclasses have a similar capacity to lower BP; however, non-DHPs appear to offer potential advantages in the management of patients with chronic kidney disease and diabetic nephropathy.^{8,9}

Dihydropyridines are among the most widely used drugs for the management of cardiovascular disease. Introduced in the 1960s, dihydropyridines have undergone several changes to optimize their efficacy and safety. Four generations of dihydropyridines are now available. The first-generation nifedipine and nifedipine have proven efficacy against hypertension. However, because of their short duration and rapid onset of vasodilator action, these drugs were more likely to be associated with adverse effects. The new second generation slow-release and short-acting preparations like benidipine, and efonidipine allowed better control of the therapeutic effect and a reduction in some adverse effects. The third-generation dihydropyridines, amlodipine and azelnidipine exhibit more stable pharmacokinetics, are less cardio-selective and, consequently, well tolerated in patients with heart failure. The fourth-generation highly lipophilic dihydropyridines, lercanidipine and lacidipine are now available which provide a real degree of therapeutic comfort in terms of stable activity, a reduction in adverse effects and a broad therapeutic spectrum, especially in myocardial ischemia and potentially in congestive heart failure.¹⁰

Ca²⁺ channel blockers have been categorized according to selectivity for the voltage-dependent Ca²⁺ channels in vascular smooth muscle against those in cardiac tissue,¹¹ chemical class, and binding affinity to receptors in Ca²⁺ channels, chemical structure, or lipophilicities.¹² In 1996, a useful classification was proposed to divide Ca²⁺ channel blockers into three groups – first, second, and third generation, which were fundamentally based on the effects on Ca²⁺ channel receptor-binding properties, tissue selectivity, and pharmacokinetic profile.¹³

4. Calcium channels and CCBs

Among antihypertensive drugs, calcium channel blockers, which inhibit L-type voltage-gated calcium channels, are

potent vasodilators, and have been used as a first- or second-line drug. Dihydropyridine-class calcium channel blockers are categorized into three generations according to the length of activity, and long-acting calcium channel blockers cause less activation of sympathetic nervous system, and are reported to offer beneficial action compared with short-action agents. Furthermore, novel types of calcium channel blockers have been developed that possess the blocking action on other calcium channel subtypes (T- and N-type), and exert agent-specific action apart from their class effects, such as the effects on heart rate and renin/aldosterone release. These additional benefits conferred by T/N-type calcium channel blockade are anticipated to provide organ protective actions in the treatment of hypertension, in addition to the blood pressure-lowering effect of L-type calcium channel blockade. In conclusion, novel calcium channel blockers with sustained activity and T/N-type calcium channel-blocking action could provide more beneficial effects than classical blockers, and may expand the clinical utility of these agents.¹⁴

The voltage-gated calcium channel consists of 4 subunits, $\alpha 1$, $\alpha 2$ - δ , β and γ . An $\alpha 1$ subunit is the dominant component of the calcium channels and constitutes pore structure for ion conduction. Ten different $\alpha 1$ subunits have been reported and each of them has specific distribution and ion conductance of its channels. These distinct subunits characterize the channel properties of L-, N-, T-, P-, Q- and R-type calcium channels.^{15,16} Of these channels, L-type calcium channels are the main targets of the CCB. Based on the chemical structure, CCBs are categorized into 3 subgroups; benzothiazepines (e.g., diltiazem and clenazem), phenylalkylamines (e.g., verapamil and gallopamil) and dihydropyridines (e.g., nifedipine, nifedipine, felodipine, amlodipine, aranidipine, azelnidipine, cilnidipine, efonidipine, manidipine and nilvadipine). The differences in chemical structures would provide heterogeneity in the action of these agents. All CCBs block the calcium influx by binding to the $\alpha 1$ subunit,¹⁷ and inhibit cell excitability. Although the CCB inhibits calcium currents through L-type calcium channels, some CCBs possess the ability to block other calcium channels (Fig. 1).

Cilnidipine has been extensively studied by researchers in its preclinical and clinical development phases. Renoprotective, neuroprotective and cardioprotective effects of cilnidipine have been demonstrated in clinical practice or animal examinations. It is noticed that cilnidipine may have pleiotropic effects besides N-type Ca²⁺ channel-blocking action. Therefore, the inhibition of N-type Ca²⁺ channels may provide a new strategy for the treatment of cardiovascular diseases. This article reviews the current understanding of the pharmacological profile and clinical utility of cilnidipine as a unique antihypertensive drug.

Cilnidipine is a recently developed CCB, and possesses both L- and N-type calcium channels blocking activity. Since N-type calcium is distributed along the nerve and in the brain, cilnidipine is anticipated to exert specific action on nerve activity, such as inhibition of the sympathetic nervous system.¹⁸ Uneyama et al demonstrated that submicro molecular concentrations of cilnidipine effectively suppressed N-type Ca²⁺ channel currents in isolated sympathetic neurons.¹⁹

They further compared the inhibitory effect of various dihydropyridines on cardiac L-type Ca²⁺ channels in isolated

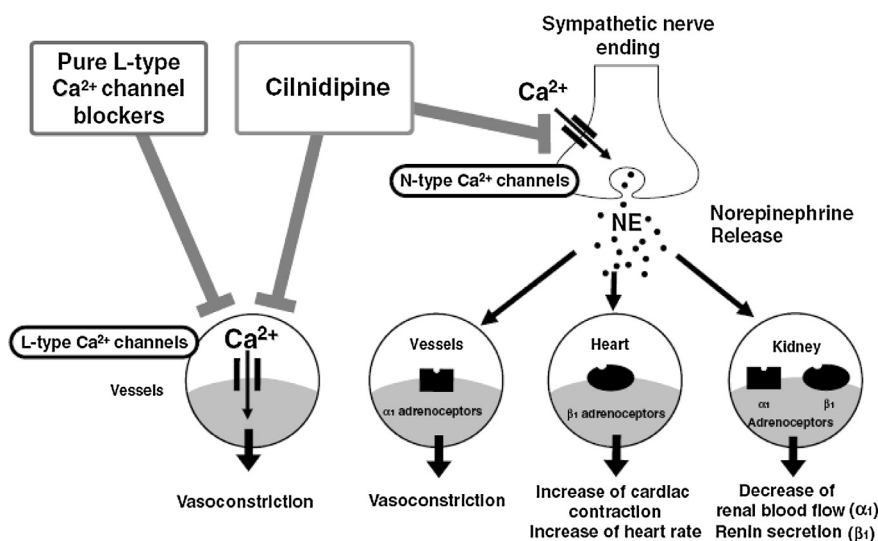


Fig. 1 – Diagrammatic representation of L/N dual action of cilnidipine.

ventricular myocytes with that on N-type Ca^{2+} channels in superior cervical ganglion neurons obtained from Wistar rats.²⁰ In that study, all dihydropyridines, except cilnidipine, showed a small inhibitory effect at a concentration of 1 μM . Furthermore, it was noted that the selectivity for L-type/N-type of Ca^{2+} channels differed markedly among the compounds tested, where nifedipine showed high selectivity for L-type Ca^{2+} channels and cilnidipine blocked both L- and N-type of Ca^{2+} channels. The N-type channel-blocking action of cilnidipine has also been confirmed by Takahara A et al in IMR-32 human neuroblastoma cells.²¹ Cilnidipine inhibits N-type Ca^{2+} channels more potently than other Ca^{2+} channel blockers and several *in vitro* studies conducted by Nap A et al (2004) have demonstrated that cilnidipine attenuates norepinephrine release from sympathetic nerve endings.^{22,23} Furthermore, such effects have been observed in *in vivo* experiments using anesthetized rats²⁴ and dogs.²⁵ The cardioprotective action of cilnidipine has been analyzed in a rabbit model of myocardial infarction, in which cilnidipine decreased the myocardial interstitial norepinephrine levels during ischemia and reperfusion periods, leading to reduction of the myocardial infarct size and incidence of ventricular premature beats.²⁶ Furthermore, *in vivo* experimental data have suggested that cilnidipine shows antianginal effects in the experimental model of vasopressin-induced angina and improvement of the ventricular repolarization abnormality in the canine model of long QT syndrome.^{27,28}

Sympatholytic profiles of cilnidipine observed in both *in vitro* and *in vivo*, are also observed in clinical practice.^{19,24} In clinical studies, conducted by Nagahama S et al (2007) and Iimura O et al (1993) the antihypertensive effect of cilnidipine has been demonstrated in hypertensive patients,²⁹ and also in patients with severe hypertension.³⁰ In a study conducted in 2920 hypertensive patients, treatment with cilnidipine and angiotensin receptor blocker showed significant reductions in heart rate, particularly in those with a higher baseline heart rate ≥ 75 beats/min, whereas there were few adverse reactions associated with central nervous functions.²⁹ Hoshida et al³¹ demonstrated that the reductions in heart rate were

significantly greater in the cilnidipine group than the amlodipine group in a 24-h ambulatory blood pressure monitoring study with hypertensive patients. Furthermore, cilnidipine has been clinically demonstrated to be effective for morning hypertension and white-coat hypertension, which is closely associated with sympathetic nerve activation.^{32,33} The CANDLE trial³⁴ and other clinical studies have demonstrated that cilnidipine improves left ventricular function.³⁵

Hypertension is one of the most important risk factors for the progression of renal disease.^{36,37} In the follow-up study of the multiple risk factor intervention trial (MRFIT), a strong, graded relation between blood pressure and end-stage renal disease was identified.³⁸ Moreover, chronic renal dysfunction,³⁹ proteinuria or albuminuria⁴⁰ are independent risk factors for cerebrovascular and cardiovascular diseases. Thus, the treatment of hypertension constitutes a crucial strategy to minimize the development of renal disease and to reduce the risk of cardiovascular events.

In clinical studies, Rose and Ikebukoro⁴¹ demonstrated that cilnidipine significantly decreased urinary albumin excretion without affecting serum creatinine concentration in hypertensive patients, which is comparable to the angiotensin converting enzyme inhibitor benazepril. Other studies conducted by Kojima S (2004) and Tsuchihashi T et al (2005) have shown that the renal protective effect of cilnidipine was greater than pure L-type Ca^{2+} channel blockers.^{42,43} Furthermore, the combination of cilnidipine and valsartan was shown to decrease the albumin/creatinine ratio more markedly than valsartan alone.⁴⁴ Recently, the multicenter, open labeled and randomized trial of Cilnidipine versus Amlodipine Randomized Trial for Evaluation in Renal disease (CARTER) has shown that cilnidipine is superior to amlodipine in preventing the progression of proteinuria in patients with hypertension and chronic renal disease when coupled with a renin–angiotensin system inhibitor.⁴⁵ Recently, prevalence of cardiovascular disease and cardiovascular mortality have been suggested to be closely associated with renal function; namely, cardio–renal connection.⁴⁶ Thus, the renal protective effects of cilnidipine may secondarily contribute to cardioprotection.

Takashi Masuda, Misao N. Ogura, Tatsumi Moriya, et al (2011) have demonstrated the beneficial effects of L- and N-type calcium channel blocker on glucose and lipid metabolism and renal function in patients with hypertension and type II diabetes mellitus.⁴⁷

A recent study by Fan et al (2011) indicates that cilnidipine relaxes human arteries through Ca^{2+} channel antagonism and increases production of nitric oxide by enhancement of endothelial nitric oxide synthase in the human internal thoracic artery.⁴⁸

Ranjan Shetty, G Vivek et al (2013) have conducted a study in 27 patients of essential hypertension with amlodipine-induced ankle edema and concluded that therapy with cilnidipine resulted in complete resolution of amlodipine-induced edema in all the cases without significant worsening of hypertension or tachycardia. Cilnidipine is an acceptable alternative antihypertensive for patients with amlodipine-induced edema.⁴⁹

Xu Guo-Liang et al (2012) conducted a meta-analysis of the efficacy and safety of cilnidipine in Chinese patients with mild to moderate essential hypertension, of 11 clinical trials and concluded that cilnidipine is a useful agent to treat mild to moderate essential hypertension.⁵⁰

5. Conclusion

Cilnidipine is a promising 4th generation Ca^{2+} channel blocker with a rational pharmacological profile; i.e. dual L/N-type Ca^{2+} channel-blocking action. The blockade of N-type Ca^{2+} channels effectively suppresses neurohumoral regulation in the cardiovascular system, including sympathetic nervous system and renin–angiotensin–aldosterone system. Thus, cilnidipine is expected to be favorable for various types of complications of hypertension. The currently described information suggests that cilnidipine is a new type of antihypertensive drug distinguished from other L-type Ca^{2+} channel blockers or even other antihypertensives, which will be useful for selection of antihypertensive drugs according to the pathophysiological condition of a patient.

Conflicts of interest

All authors have none to declare.

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