Cilnidipine, a Dual L/N-type Ca\textsuperscript{2+} Channel Blocker in Hypertension Management: A Review

Ketan K Mehta\textsuperscript{1}, Mangesh Tiwaskar\textsuperscript{2}, Prabhu Kasture\textsuperscript{3}\*  
Received: 17 November 2023; Accepted: 30 November 2023

Abstract

Calcium channel blockers (CCBs) are widely used antihypertensive agents due to their effectiveness in reducing blood pressure (BP), along with their good tolerability and evidence of reducing hypertension (HTN)—related cardiovascular and renal diseases. Cilnidipine, a unique dihydropyridine calcium antagonist, exhibits potent inhibitory action on both N-type and L-type voltage-dependent calcium channels. With excellent oral absorption and a prolonged duration of action, it demonstrates a significant antihypertensive effect. It effectively reduces BP both systolic and diastolic while providing renal, neurological, and cardiovascular protection. Unlike L-type CCBs, cilnidipine does not increase pulse rates (PRs) and is associated with reduced occurrence of pedal edema. Cilnidipine is an effective treatment choice for individuals with mild to moderate essential HTN, whether it is administered alone or in conjunction with other treatment modalities.

Overview

Hypertension (HTN) increases the risk of developing major cardiovascular, cerebrovascular, and renal complications significantly. The risk of developing complications can be significantly reduced and the cardiovascular prognosis can be improved through the effective treatment of HTN.

Within the drug class used to treat HTN, calcium channel blockers (CCBs) exhibit distinct variations in their pharmacokinetic and pharmacodynamic properties, selectivity, and duration of pharmacological action. However, it is noteworthy that their interaction with L-type voltage-dependent transmembrane calcium channels remains consistent. These differences have an influence on the clinical and therapeutic efficacy, tolerability, and safety characteristics in various clinical environments.\textsuperscript{1}

Cilnidipine, a fourth-generation CCB, stands out as a distinctive medication due to its inhibitory effects on both the sympathetic N-type and L-type calcium channels. This unique characteristic is attributed to its actions on sympathetic neurotransmitter release. Through its distinct mechanism of action on sympathetic N-type Ca\textsuperscript{2+} channels, it decreases the release of norepinephrine, resulting in vasodilation, a reduction in heart rate, and an elevation in renal blood flow. Its antihypertensive and cardio/kidney/neuroprotective effects have been reported in preclinical and clinical trials.\textsuperscript{2}

As per the JNC 8 recommendations, CCB is recommended as initial therapy in patients with HTN, including those with diabetes.\textsuperscript{3} The management of HTN in patients with diabetes mellitus, as per the Research Society for the Study of Diabetes in India (RSSDI) guidelines, suggests the use of cilnidipine. This novel molecule is considered to be more effective and safer than conventional CCBs for Indian diabetic hypertensive patients. Cilnidipine is the recommended choice among other CCBs for individuals with diabetes and HTN due to its kidney and heart-protective effects and improved safety and tolerability profile, specifically in relation to pedal edema.\textsuperscript{4}

Advantages of Two-pronged Approach with Cilnidipine

Cilnidipine, a combined L- and N-type calcium channel blocker (dual L/N-type Ca\textsuperscript{2+} channel-blocking action) with its two-pronged approach has been proven to be more effective and safer in managing HTN.\textsuperscript{5,6} The inhibition of N-type Ca\textsuperscript{2+} channels efficiently hinders the neurohumoral control in the cardiovascular system, encompassing the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS).\textsuperscript{6,7} Blocking the L-type Ca\textsuperscript{2+} channel results in the dilatation of peripheral resistance vessels, while inhibiting the N-type Ca\textsuperscript{2+} channels in neurons disrupts the sympathetic nervous outflow. This disruption leads to a decrease in plasma catecholamine levels, which in turn causes additional vasodilatation. The vasodilatation of pre- and postcapillary resistance vessels leads to a decrease in capillary HTN resulting in excessive filtration of fluid into the interstitium.\textsuperscript{8}

Cilnidipine is anticipated to be beneficial for a range of complications linked to HTN.\textsuperscript{5,7} The remarkable antihypertensive efficacy and low incidence of ankle edema can be attributed to its dual mechanisms of action (Fig. 1).\textsuperscript{3,10}

Cilnidipine is a first-line CCB that can effectively manage HTN either as a standalone treatment or as part of a combined therapy.\textsuperscript{11}

- Is a newer dihydropyridine CCB, an L/N-type dual CCB, proven to have a long-lasting antihypertensive effect that has been in clinical use since 1995.
- Demonstrates a prolonged duration of effectiveness in lowering blood pressure (BP) despite a shorter half-life (7.5 hours) and a high protein binding (98%).
- Effectively lowers both systolic blood pressure (SBP) and diastolic blood pressure (DBP) without causing any elevation in pulse rates (PR) or plasma catecholamines.
- Demonstrates consistent antihypertensive efficacy with minimized negative consequences.
- Equal in effectiveness to L-type CCB in reducing BP with lower incidence of pedal edema in people with HTN.
- Extensively researched in controlling high BP and has demonstrated efficacy in providing renal protection, neuroprotection, and cardioprotection.

Cilnidipine: An Effective Antihypertensive

Cilnidipine is a potent antihypertensive medication used to treat mild-to-moderate essential HTN. It exhibits similar antihypertensive properties as other first-line antihypertensive drugs.\textsuperscript{12} Patients with HTN can have a significant and sustained decrease...
Cilnidipine, a Dual L/N-type Ca$^{2+}$ Channel Blocker in HTN Management

Cilnidipine, a Dual L/N-type Ca$^{2+}$ Channel Blocker in HTN Management

Journal of the Association of Physicians of India, Volume 72 Issue 4 (April 2024)

55

and morning surge, while also effectively reducing the whitecoat effect in individuals with essential HTN.

The morning BP measured at home and the BP measured at the office, which was not well controlled initially (146 ± 11/89 ± 7 mm Hg and 146 ± 17/88 ± 11 mm Hg, respectively) (Figs 2A and B), showed a significant reduction (both $p < 0.001$). In 8 weeks, the morning SBP values of currently treated patients were successfully lowered to the desired level of < 135 mm Hg in 58% of cases. Additionally, 80% of new patients achieved the target level with the once-daily administration of cilnidipine, resulting in a decrease in PR. Furthermore, the administration of cilnidipine also significantly reduced the whitecoat effect (Fig. 3).

Cilnidipine effectively mitigates the whitecoat effect in patients with HTN by inhibiting the N-type voltage-dependent calcium channel. Moreover, it proves to be advantageous for the long-term management of HTN.

In a comprehensive evaluation and meta-analysis of randomized controlled trials (RCTs) conducted among Chinese patients (total of 11 RCTs, $n = 790$) by Xu et al., cilnidipine was reported to have the same antihypertensive effects compared to first-line antihypertensive in managing patients with mild to moderate essential HTN. Cilnidipine has the ability to decrease arterial BP and total peripheral resistance while having no impact on heart rate, cardiac index, or cardiovascular structure.

Efficient for Treating Morning Hypertension and Whitecoat Hypertension

Cilnidipine demonstrates efficacy in patients with HTN who experience morning HTN as a result of possible overactivity of the sympathetic nerves. It is known to greatly reduce BP during sleep when there is an excessive activation of the sympathetic nerve. Cilnidipine proves to be a valuable medication for managing morning HTN and morning surge, while also effectively reducing the whitecoat effect in individuals with essential HTN.

The morning BP measured at home and the BP measured at the office, which was not well controlled initially (146 ± 11/89 ± 7 mm Hg and 146 ± 17/88 ± 11 mm Hg, respectively) (Figs 2A and B), showed a significant reduction (both $p < 0.001$). In 8 weeks, the morning SBP values of currently treated patients were successfully lowered to the desired level of < 135 mm Hg in 58% of cases. Additionally, 80% of new patients achieved the target level with the once-daily administration of cilnidipine, resulting in a decrease in PR. Furthermore, the administration of cilnidipine also significantly reduced the whitecoat effect (Fig. 3).

Cilnidipine effectively mitigates the whitecoat effect in patients with HTN by inhibiting the N-type voltage-dependent calcium channel. Moreover, it proves to be advantageous for the long-term management of HTN.

In a comprehensive evaluation and meta-analysis of randomized controlled trials (RCTs) conducted among Chinese patients (total of 11 RCTs, $n = 790$) by Xu et al., cilnidipine was reported to have the same antihypertensive effects compared to first-line antihypertensive in managing patients with mild to moderate essential HTN. Cilnidipine has the ability to decrease arterial BP and total peripheral resistance while having no impact on heart rate, cardiac index, or cardiovascular structure.

![Dual mechanisms of action of cilnidipine](image1)

**Fig. 1:** Dual mechanisms of action of cilnidipine

**Figs 2A and B:** Morning BP at home and office BP and PR before and after cilnidipine administration in (A) currently treated patients; (B) newly diagnosed patients and after cilnidipine administration in (A) currently treated patients; (B) newly diagnosed patients. DBP, diastolic blood pressure; SBP, systolic blood pressure; values are expressed as the mean ± SD. ***, $p < 0.001$ vs. before administration, and #, $p < 0.05$ vs. home blood pressure or home PR in the morning.

Efficient for Treating Morning Hypertension and Whitecoat Hypertension

Cilnidipine demonstrates efficacy in patients with HTN who experience morning HTN as a result of possible overactivity of the sympathetic nerves. It is known to greatly reduce BP during sleep when there is an excessive activation of the sympathetic nerve. Cilnidipine proves to be a valuable medication for managing morning HTN and morning surge, while also effectively reducing the whitecoat effect in individuals with essential HTN.

The morning BP measured at home and the BP measured at the office, which was not well controlled initially (146 ± 11/89 ± 7 mm Hg and 146 ± 17/88 ± 11 mm Hg, respectively) (Figs 2A and B), showed a significant reduction (both $p < 0.001$). In 8 weeks, the morning SBP values of currently treated patients were successfully lowered to the desired level of < 135 mm Hg in 58% of cases. Additionally, 80% of new patients achieved the target level with the once-daily administration of cilnidipine, resulting in a decrease in PR. Furthermore, the administration of cilnidipine also significantly reduced the whitecoat effect (Fig. 3).

Cilnidipine effectively mitigates the whitecoat effect in patients with HTN by inhibiting the N-type voltage-dependent calcium channel. Moreover, it proves to be advantageous for the long-term management of HTN.

In a comprehensive evaluation and meta-analysis of randomized controlled trials (RCTs) conducted among Chinese patients (total of 11 RCTs, $n = 790$) by Xu et al., cilnidipine was reported to have the same antihypertensive effects compared to first-line antihypertensive in managing patients with mild to moderate essential HTN. Cilnidipine has the ability to decrease arterial BP and total peripheral resistance while having no impact on heart rate, cardiac index, or cardiovascular structure.
Cilnidipine, a Dual L/N-type Ca\textsuperscript{2+} Channel Blocker in HTN Management

The clinical utility of cilnidipine lies in its ability to exert sympathoinhibitory effects and achieve balanced vasodilation of both arteries and veins. This makes it an effective and achieve balanced vasodilation of both ability to exert sympathoinhibitory effects.

The contrasting nature of cilnidipine’s antisympathetic effects sets it apart from other Ca\textsuperscript{2+} channel blockers.\textsuperscript{7} Besides the N-type Ca\textsuperscript{2+} channel-blocking action, it has pleiotropic effects. It is found to have renoprotective, cardioprotective and neuroprotective in preclinical and clinical studies.\textsuperscript{6}

**Pleiotropic Effects of Cilnidipine**

The contrasting nature of cilnidipine’s antisympathetic effects sets it apart from other Ca\textsuperscript{2+} channel blockers.\textsuperscript{7} Besides the N-type Ca\textsuperscript{2+} channel-blocking action, it has pleiotropic effects. It is found to have renoprotective, cardioprotective and neuroprotective in preclinical and clinical studies.\textsuperscript{6}

**Renoprotective Effects**

L/N-type CCBs exhibit sympatholytic properties and offer renal protection by dilating both afferent and efferent arterioles of the renal glomerulus. This mechanism provides a stronger shield against organ damage caused by HTN when compared to L-type CCBs.\textsuperscript{22,23} Cilnidipine has been found to exhibit superior effects in reducing proteinuria progression among hypertensive patients when compared to L-type CCBs.\textsuperscript{11} The activation of the ACE2/Ang(1–7) pathway and the suppression of the ACE-Ang II–angiotensin II type 1 receptor pathway are responsible for the renoprotective effect of cilnidipine.\textsuperscript{24}

The greater renoprotective effect of cilnidipine is probably due to its antioxidative properties.\textsuperscript{11,23} Cilnidipine is known to induce a more pronounced inhibition of proteinuria escalation and a greater decrease in glomerular filtration rate (GFR). Additionally, it demonstrates similar effects to renin–angiotensin inhibitors.\textsuperscript{25} It has comparable effects on serum creatinine and eGFR in hypertensive patients while being more efficient in reducing proteinuria or preventing its progression compared to L-type CCBs.\textsuperscript{26}

Cilnidipine has been found to possess antihypertensive effects comparable to L-type CCBs in individuals diagnosed with chronic kidney disease (CKD). By transitioning from an L-type CCB to cilnidipine, renal functions can be improved and proteinuria reduced. However, the reverse switch is not found to yield the same results.\textsuperscript{27-29}

Cilnidipine is recognized as a distinctive CCB capable of halting the advancement of diabetic nephropathy in individuals with type 2 diabetes and HTN.\textsuperscript{30} It may prove to be a valuable additional therapy in cases where only the administration of RAS inhibitors proves inadequate in lowering BP or reducing proteinuria.\textsuperscript{31} Cilnidipine exhibits great potential for treating HTN and hyperuricemia in patients with CKD. It effectively lowers the production of uric acid without any negative impact on the serum uric acid level. Following a switch to cilnidipine, patients with increased urinary uric acid excretion (urinary uric acid/creatinine of \(0.50\) g/g) showed a noticeable reduction of approximately \(0.1\) g/g in the urinary uric acid/creatinine ratio.\textsuperscript{32}

Cilnidipine has been proven to be a safe and effective treatment for Indian patients with mild-to-moderate HTN and type 2 diabetes mellitus. It has shown significant results in reducing both SBP and DBP, as well as microalbuminuria. After 6 months of treatment, the mean SBP decreased from 150.07 ± 5.44 to 123.03 ± 5.23 mm Hg, the mean DBP decreased from 95.5 ± 8.15 to 80.8 ± 2.42 mm Hg, and microalbuminuria decreased from 66.62 ± 8.39 to 38.8 ± 6.45 mg/L. The overall mean reduction in microalbuminuria was 27.56 ± 10.25 mg/L.\textsuperscript{33}

**Cardioprotective Effects**

A prolonged risk of cardiovascular mortality is linked to an elevated heart rate, regardless of other factors that contribute to heart disease. The conventional dihydropyridine calcium antagonists commonly cause adverse effects such as increased PR, increased sympathetic activity, and reflex tachycardia due to a decrease in BP.\textsuperscript{17}

Cilnidipine effectively reduces cardiac sympathetic overactivity in patients with essential HTN, without inducing coronary sympathetic hypertonia in response to BP reduction, which sets it apart from L-type CCBs.\textsuperscript{34} Additionally, cilnidipine’s N-type calcium channel blockade does not lead to reflex tachycardia, making it a beneficial alternative.\textsuperscript{17} Cilnidipine has also shown efficacy in improving arterial stiffness in individuals with essential HTN.\textsuperscript{22}

Cilnidipine effectively reduces vascular endothelial dysfunction and is beneficial in the long-term treatment of cardiovascular disorders.\textsuperscript{11} Cilnidipine has been recognized for its ability to inhibit excessive cardiac sympathetic activity through the blockade of N-type calcium channels. Additionally, it has been shown to enhance left ventricular (LV) diastolic function in individuals with hypertensive heart disease (HHD).\textsuperscript{35}

Patients with HHD witness significant improvements in their LV diastolic function and cardiac sympathetic activity after 6 months of treatment, with no alterations in the LV mass.\textsuperscript{35}

Cilnidipine has been recognized for its ability to enhance LV systolic function in patients with HTN, regardless of any BP alterations.\textsuperscript{36} The response to cilnidipine treatment in patients with essential HTN shows a biphasic pattern in LV diastolic performance. Initially, there is an increase in early diastolic transmural flow velocity, followed by a later increase in early diastolic LV wall motion velocity, resulting in improved LV relaxation. This finding is suggestive of cilnidipine’s positive impact on LV diastolic function in patients with essential HTN.\textsuperscript{37}
Cilnidipine, a Dual L/N-type Ca²⁺ Channel Blocker in HTN Management

Neuroprotective Effects
Cilnidipine, which inhibits the N-type calcium channels, exhibits a lower variability in BP and proves to be a more advantageous option for managing BP in patients with cerebrovascular disease when compared to other CCBs. In a study conducted by Nishioka et al., the 24-hour BP variability was assessed in 309 patients who had a previous cerebrovascular disease and were undergoing treatment with either an ACE inhibitor, ARB, β-blocker, or CCB. Among the different CCBs examined, cilnidipine was observed to have a higher occurrence of reducing BP variability. This finding suggests that cilnidipine may be more effective in stabilizing BP levels.

Aoki et al. conducted a large-scale prospective postmarketing, real-world study in Japan to evaluate the effectiveness of cilnidipine in treating uncontrolled BP in poststroke hypertensive patients. The study included 2,667 patients (60.4% male; mean age 69.0 ± 10.9 years). The results showed that cilnidipine was effective in reducing BP and was well tolerated. The proportion of patients who achieved well-controlled BP (<140/90 mm Hg) increased from 21.5 to 65.3% with cilnidipine treatment. The efficacy of cilnidipine was consistent across different clinical subtypes of stroke. This study highlights the potential of cilnidipine as a treatment option for poststroke HTN.

Cilnidipine in Combination Therapy
Use of a combination of a CCB and an ARB is widely recognized as the standard approach for treating HTN. Cilnidipine is a potent antihypertensive medication that effectively inhibits the progression of CKD and reduces the risk of cardiovascular complications when used in combination with RAS inhibitors.

The combination of cilnidipine and ARB can lead to improved renoprotective effects in hypertensive patients. This is achieved through a reduction in urinary albumin excretion and an increase in the ratio of Ang(1–7) to Ang II in plasma.

Safety and Tolerability of Cilnidipine
Ankle edema, a frequently occurring side effect of L-type CCBs caused by dilatation of precapillary vessels, is aesthetically unappealing and may lead to reduced adherence to medication and discontinuation of treatment. Cilnidipine, by blocking both N- and L-type channels, induces dilatation in both pre- and postcapillary vessels, which limits fluid filtration and consequently reduces pedal edema. Moreover, cilnidipine does not elevate heart rate as it inhibits sympathetic activity via the N-type calcium channel. Cilnidipine proves to be a reliable and safe option for managing essential HTN (Table 1), with improved patient adherence and reduced rates of treatment discontinuation.

Table 1: Cilnidipine use in HTN management

| Novel and unique CCB | Inhibits sympathetic N-type Ca²⁺ channels in addition to vascular L-type Ca²⁺ channels. Advantageous over other L-type CCBs—less influence on HR and autonomic nervous system causing less tachycardia. Favorable for various types of complications of HTN. Better safety and tolerability vs L-type CCBs with reduced proteinuria and pedal edema.
| A lesser degree of RAAS activation | Superior organ protection in addition to anti-albuminuric effect.
| Greater antiproteinuria effect | Superior to L-type CCBs in preventing the progression of proteinuria in HTN patients when coupled with an RAS inhibitor.
| Efficient antihypertensive with convenience of dosing | Administered once daily is an efficient antihypertensive regardless of the time of dosing; without reflex tachycardia; and no increase in sympathetic nervous activity compared to other CCBs.

Conclusion
Cilnidipine is distinguished from other L-type CCBs and other antihypertensive agents in that it suppresses sympathetic N-type Ca²⁺ channels alongside vascular L-type Ca²⁺ channels, leading to harmonious vasoconstriction of both arteries and veins. This attribute proves to be beneficial in the treatment of patients with HTN. At therapeutic dosages, it offers good BP regulation and its antihypertensive effects are comparable to other primary antihypertensive medications. The usual recommended dosage is 5–10 mg/day, which can be increased to a maximum of 20 mg/day. It causes a gradual and prolonged reduction in BP without triggering an increase in heart rate. It serves as a superior option for individuals experiencing heightened sympathetic activity, proteinuria, or pedal edema. The inhibition of N-type Ca²⁺ channels effectively hinders the neurohumoral regulation within the cardiovascular system, encompassing the sympathetic nervous system and the RAAS. This blockade proves advantageous in managing diverse complications associated with HTN.

References
Cilnidipine, a Dual L/N-type Ca\(^{2+}\) Channel Blocker in HTN Management


