

Cilnidipine - Novel Dual Acting Calcium Channel Blocker

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ABSTRACT

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Calcium Channel Blockers (CCBs) mainly act by vasodilatation and reduction in peripheral vascular resistance. They are one of the most commonly used drugs for the management of systemic hypertension and angina. CCBs are a heterogeneous group of drugs that can chemically be classified into dihydropyridines (DHPs) and the non – DHPs. Their common pharmacologic property is selective inhibition of L – type calcium channel opening in vascular smooth muscle and in the myocardium.

Cilnidipine is a novel and unique 1, 4 – dihydropyridine derivative developed in Japan. Most of the studies with drug are from Japan. It is not approved by US FDA and is not marketed in the US and European countries. It is a dual action calcium channel blocker with action on both L/ N type of calcium channels. It lowers blood pressure by inhibiting L – type calcium channels directly associated with vascular tone. It also inhibits N – type calcium channels, suppressing sympathetic over activity.

Being lipophilic, Cilnidipine has prolonged duration of action and once daily dose effectively control blood pressure throughout 24 hours.

It is indicated in the treatment of Essential hypertension, as monotherapy as well as in combination with other drugs. It is useful in elderly hypertensives and in those with diabetes and albuminuria. It is increasingly used in individuals with chronic kidney disease, alone or in combination with ACE inhibitors/ ARB.

Keywords: Cilnidipine, Long duration action, Indications.

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INTRODUCTION

Calcium Channel Blockers (CCBs) mainly act by vasodilatation and reduction in peripheral vascular resistance. They are one of the most commonly used drugs for the management of systemic hypertension and angina. CCBs are a heterogeneous group of drugs that can chemically be classified into dihydropyridines (DHPs) and the non – DHPs. Their common pharmacologic property is selective inhibition of L – type calcium channel opening in vascular smooth muscle and in the myocardium. DHP agents have more vascular selectivity than non – DHP agents. Non DHP agents like Verapamil and Diltiazem have more powerful effect on the myocardium and the conduction system. They have negative inotropic effect and have an inhibitory effect on the AV node and the SA node. They resemble beta blockers in their therapeutic action. The DHPs like Nifedipine and Amlodipine are powerful vasodilators but have no significant effect on the myocardium and the conduction system. They tend to produce reflex stimulation of the sympathetic system and tend to augment the heart rate. This action

is more pronounced with the immediate release short acting DHPs like Nifedipine which are seldom used now. Reflex sympathetic stimulation is less pronounced with slow acting preparations and with long acting DHPs like Amlodipine.

Calcium Channels:

Calcium channels are classified into at least six subtypes namely L, N, P, Q, R and T – type, based on electrophysiological and pharmacological evidence. The T – type calcium channels are known as low voltage activated calcium channels. The other five types of calcium channels are all high voltage activated calcium channels, which depolarize at approximately – 40 mV. The most important property of all CCBs is selective inhibition of inward flow of charge bearing calcium ions when the calcium channel is permeable. The conventional long – lasting opening calcium channel is termed the L – type channel, which is blocked by CCBs and increased in activity by catecholamines. The function of the L – type channel is to admit the substantial amount of calcium ions required for initiation of contraction via calcium induced calcium release from the sarcoplas-

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mic reticulum. In the cardiovascular system, L – type calcium channels are predominantly expressed in the heart and blood vessels. The “Transient” T – type channel opens at more negative potentials than the L – type channels. It plays an important role in the initial depolarization of SA nodal and AV nodal tissue. N type calcium channels are localized at the nerve endings in the sympathetic and central nervous systems, which regulate the release of neurotransmitters. In experimental studies, N – type calcium channels are shown to contribute about 85% of all calcium currents in the sympathetic neurons.

Classification of CCBs according to effects on Sympathetic function:

Nifedipine, the prototypical DHP can be considered the first generation agent. It has no effect on the N – type calcium channels. The immediate release preparation produces profound vasodilatation and reflex tachycardia due to sympathetic stimulation. The plasma Norepinephrine levels are increased. These effects are partly alleviated by slow release formulations.

DHPs like Benidipine, Efonidipine and Nitrendipine are categorized as second generation agents and they induce vasodilator action more slowly than Nifedipine. This kinetic profile is explained by slow association and/ or dissociation rates of drugs for L – type calcium channels. The effect on heart rate is negligible. There is no evidence that these drugs have anti sympathetic or N – type calcium channel blocking property.

Amlodipine and Azelnidipine are classified as third generation agents. Amlodipine has a unique pharmacokinetic profile with slow onset of action and $t_{1/2}$ of almost 36 hours. Reflex stimulation of the sympathetic nervous system is significantly less compared to previous generation DHPs. In isolated aortic preparation of rabbits, amlodipine has no effects on catecholamine release evoked by electrical stimulation of perivascular nerves. Studies have consistently demonstrated that an anti hypertensive dose of Amlodipine increases heart rate together with elevation of plasma norepinephrine concentration due to reflex sympathetic stimulation. No effects on the N – type channels have been demonstrated.

Cilnidipine is a novel and unique 1, 4 – dihydropyridine derivative developed in Japan. Most of the studies with drug are from Japan. It is not approved by US FDA and is not marketed in the US and European countries. It is a dual action calcium channel blocker with action

on both L/ N type of calcium channels. It lowers blood pressure by inhibiting L – type calcium channels directly associated with vascular tone. It also inhibits N – type calcium channels, suppressing sympathetic over activity. Cilnidipine demonstrated reduction in norepinephrine levels without affecting neurohormonal status. Experimental studies have demonstrated that Cilnidipine has ability to reduce ventricular premature beats, myocardial interstitial norepinephrine levels and has an inhibitory effect on platelet function. The cardio protective 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 models, leading to reduction of the myocardial infarct size and incidence of ventricular arrhythmias.

The calcium channel blockers in general tend to selectively dilate the glomerular afferent arteriole and the pre capillary sphincter. Because it has no significant effect on the efferent arteriole, the intra glomerular pressure tends to increase. This can be deleterious as it can worsen proteinuria. The absence of dilatation of the post capillary sphincter is responsible for the pedal oedema very often observed with CCBs. The ACE inhibitors and ARBs have an opposite effect. They tend to selectively dilate the glomerular efferent arteriole and tend to reduce the intra glomerular pressure and reduction in proteinuria. The beneficial effect of ACE inhibitors and ARBs in proteinuria is because of its selective effect on the efferent arteriole. Combination of ACE inhibitors/ ARBs with CCBs produce less pedal edema compared to CCBs alone. With the combination, both pre and post capillary sphincters are dilated and hence transudation of fluids does not readily happen. Treatment with DHPs like Amodipine or Nifedipine without ACEIs/ ARBs can worsen proteinuria. In contrast to this Cilnidipine because of its effect on N – type calcium channels has been shown to produce dilatation of both afferent and efferent arterioles in the glomeruli and hence does not lead to intra glomerular hypertension and worsening of proteinuria. In fact, combination of ACEIs/ ARBs with Cilnidipine is more effective in reducing proteinuria than either agent alone. Because of the same reason, pedal oedema is significantly less with Cilnidipine compared with the conventional CCBs which do not have an effect on the N – type calcium channels.

Insulin resistance and Glucose intolerance are important issues to be considered in the total evaluation of a patient with essential hypertension. “New – onset diabetes” as a complication of long term treatment with

beta blockers and diuretics are increasingly recognized. In studies Cilnidipine has been shown to improve insulin sensitivity by 21% when used in essential hypertension. No adverse effects on serum lipids have been demonstrated.

Being lipophilic, Cilnidipine has prolonged duration of action and once daily dose effectively control blood pressure throughout 24 hours. This has been demonstrated in ambulatory BP recordings.

Clinical Pharmacokinetics:

Cilnidipine is metabolized by both liver and kidney. It is rapidly metabolized by liver microsomes by dehydrogenation process. The CYP 3A is a major CYP 450 isoform involved in the dehydrogenation of the dihydropyridine ring. Inhibitors of CYP 3A can lower the rate of Cilnidipine metabolism and increase the level of Cilnidipine in the body. 20% of Cilnidipine is eliminated through the urine and 80% is eliminated through faeces.

Indications:

It is indicated in the treatment of Essential hypertension, as monotherapy as well as in combination with other drugs. It is useful in elderly hypertensives and in those with diabetes and albuminuria. It is increasingly used in individuals with chronic kidney disease, alone or in combination with ACE inhibitors/ ARB. Though it is useful in patients with Coronary heart disease and angina, only limited data is available to justify routine use.

Cilnidipine has been clinically demonstrated to be effective for morning surges of hypertension and for “white – coat hypertension”, both of which are associated with sympathetic stimulation.

Side effects and contraindications:

Significant side effects are uncommon. Palpitation, tachycardia and pedal oedema are less compared to Nifedipine and Amlodipine because of the inhibition of the N – type calcium channels. It should be used with caution in patients with significant Aortic stenosis. Safety in pregnancy is not established. It is contraindicated in individuals with hypersensitivity to the drug.

Dosage and administration:

The usual starting dose is 5 to 10 mg once daily. As per WHO, the prescribed average dose is 10 mg daily. The dose can be stepped upto 20 mg if required. It can be safely combined with other classes of drugs including

ACE inhibitors, ARBs, beta blockers, diuretics and alpha blockers. Combination of Cilnidipine with thiazide diuretic may have less than additive anti hypertensive effects. Cilnidipine with ACEI or ARB is an excellent combination because of the reno protective and vasculo protective effects and because of the significantly less incidence of peripheral oedema.

CONCLUSION

Cilnidipine is a novel dihydropyridine calcium channel blocker with a dual mechanism of action. It acts on both L and N – type calcium channels. It has all the advantages of a long acting vasculo selective DHP calcium channel blocker. It is as effective as Amlodipine and long acting Nifedipine in controlling blood pressure. Being a new drug, outcome data are not available. In addition, it inhibits cardiac sympathetic over activity and prevents reflex tachycardia. Cilnidipine is useful in patients with effort angina but only limited data are available. It tends to reduce intra glomerular pressure and has a protective effect on proteinuria unlike Amlodipine. It improves insulin sensitivity without altering lipid levels. It has a salutary effect on endothelial dysfunction and may help in regression of atherosclerosis. Utility of this drug in diabetic and elderly hypertensives is well established. It is devoid of major side effects and peripheral oedema is usually not a problem, unlike other dihydropyridine CCBs. Because of the several advantages, Cilnidipine is increasingly prescribed in clinical practice.

END NOTE

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