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Role of Cilnidipine in the Management of Essential Hypertension

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Abstract: Large numbers of drugs are used in the treatment of hypertension and Calcium Channel Blockers are an important group among them. Cilnidipine is a new calcium channel blocking drug distinguished from other L-type calcium channel blockers with additional N-type of calcium channel blocking property. Cardioprotective, renoprotective and neuroprotective action of cilnidipine can provide additional benefit in form of reduced morbidity in the management of hypertension by controlling sympathetic over activity.
Keywords: Hypertension, L-type calcium channel blockers, N-type Calcium Channel Blocking property, sympathetic over activity, Cilnidipine.

INTRODUCTION

Hypertension is a multifactorial disease in which elevated blood pressure is merely a sign of underlying multiple physiological abnormalities. One of the major factors implicated in the onset of hypertension is the over activity of sympathetic nervous system. Hypertension is an important risk factor for various diseases, including dementia, haemorrhagic and ischemic stroke, ischemic heart disease, chronic kidney disease, heart failure and dissecting aneurysm of the aorta. It is one of the under-diagnosed and under-treated medical conditions all over the world. High dietary intake of sodium, stressful lifestyle and smoking may predisposes an individual to hypertension. High blood pressure can occur at any age but is particularly prevalent in people with a family history of hypertension, preexisting vascular disease, person with obesity, diabetes, chronic smokers and heavy drinkers [1].

Antihypertensive drugs

Various classes of antihypertensive drugs have been in the market, including diuretics, α -blockers, β -blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), calcium channel blockers (CCBs) and others. These drugs are being used for the treatment of hypertension either alone or in combination. Each antihypertensive agent has its specific indications, therapeutic efficacies and limitations.

The goal of antihypertensive therapy is to reduce systemic morbidity and mortality. Increased sympathetic activity is the hallmark of cardiovascular complications associated with hypertension. Julius described a hyperkinetic state, in which both cardiac output and heart rate are elevated, five times more frequently in patients with borderline hypertension than in the normotensive population [2]. A higher mean nor-epinephrine level is observed in hypertensive individuals. Epinephrine enhances platelet activation, and this effect is pronounced in hypertensive individuals, who are therefore at increased risk of coronary thrombosis. Hyperactive sympathetic system in setting of hypertension often triggers complications like ischemic heart disease, strokes, heart failure and renal failure. Thus in clinical practice it is important to focus on controlling the sympathetic over activity along with effective reduction of high blood pressure.

Calcium channel antagonists

Voltage-sensitive Ca^{2+} channel mediate the entry of extracellular Ca^{2+} into smooth muscle and cardiac myocytes and sinoatrial and atrioventricle nodal cells in response to electrical depolarization. An increased concentration of cytosolic Ca^{2+} causes increased contraction in cardiac and vascular smooth muscle cells. The Ca^{2+} channel antagonists produce their effects by binding to the α1 subunit of the L – type $Ca2^{+}$ channels and reducing $Ca2^{+}$ flux through the channel.

Voltage gated calcium channels are made up of 4 subunits - α1, α2-δ, β and γ based on their conductance and sensitivity to voltage. All Ca^{2+} channel blockers bind to α1 subunit of the L type Ca^{2+} channel. This is the main pore forming structure for ion conduction. It has at least 10 different subtypes, that have been cloned and classified into three subfamilies: Cav1.x; Cav2.x; and Cav3.x, based on their gene

sequence similarity. Tissue specificity of the calcium channel and time for ion conduction; is dependent on the subtype of α1 subunit. According to this the voltage dependent calcium channels are of L-, N-, P-, Q-, R- and T- type. T-type of Ca^{2+} channels are example of low-voltage-activated (LVA) Ca^{2+} channels which activate and deactivate slowly, but inactivate rapidly. The other five types of Ca^{2+} channels are all high-voltage-activated (HVA) Ca^{2+} channels, which depolarize at approximately −40 mV. In the cardiovascular system, L-type Ca^{2+}channels are predominantly expressed in the heart and vessels, and regulate vascular tone, sinus nodal function and cardiac contractility. Thus, the channel has been recognized as pharmacological target for the treatment of cardiovascular disease [3].

Based on their chemical structure, CCBs are classified into 3 subgroups; benzothiazepine (e.g., diltiazem and clenazem), phnenylalkylamines (e.g., gallopamil and verapamil) and dihydropyridines (e.g., nifedipine, nicardipine, nimodipine, felodipine, amlodipine, azelnidipine, lercanidipine, lacidipine and cilnidipine). Heterogeneity in the action of these agents is due to the difference in chemical structures. All classes of CCBs inhibit calcium currents through L-types of calcium channels and some have additional effects of blocking other types of calcium channel. All CCBs share a final common effect but the manner in which they exert their pharmacological action is different between subclasses. While Dihydropyridine (DHP) CCBs tends to be more potent vasodilators, the non – dihydropyridine (non-DHP) agents are marked negative inotropic [4].

Calcium channel blockers (CCBs) are among the commonly marketed antihypertensive medications and are especially effective in the management of hypertension in elderly who frequently have large-vessel stiffness. They inhibit L-type of voltage-gated calcium channels in the vasculature and myocardium to reduce smooth muscle and cardiac contractility and decrease total peripheral resistance and cardiac output.

Dihydropyridines are one of the widely used medicines of cardiovascular disease management. A working classification of CCBs was proposed on 1996 based on calcium channel receptor binding properties, tissue selectivity and pharmacokinetic profile. Since its introduction in 1960s, dihydropyridines underwent several changes to optimize their safety and efficacy and currently they are in their 4th generation. Nifedipine and Nicardipine are the first generation DHPs with established efficacy as antihypertensive but due to their rapid onset and short duration of vasodilatory properties they were more likely to be associated with adverse effects. The second generation felodipine and nimodipine are short acting but slow release preparation, which allowed better therapeutic control and reduction of some side effects. More suitable pharmacokinetic preparations like amlodipine and azelnidipine are of third generation and are less cardio selective and consequently better tolerated in patients with heart failure [5]. However, such pharmacokinetic and pharmacodynamic improvements do not always overcome reflex sympathetic action induced due to the hypotensive effect of L-type Ca^{2+} channel blockers [6].

L-type of voltage –gated calcium channel blockers are potent vasodilators and often used as a first or second line drug in management of hypertension. Longer acting DHP-CCBs causes less reflex activation of sympathetic nervous system and are reported to be beneficial than the short acting formulations. Novel type of calcium channel blockers have been developed which have additional properties of blocking T and N subtypes of calcium channels and apart from their class effects they exerts specific action on heart rate and renin aldosterone system. In addition to blood pressure lowering effects these novel drugs are anticipated to provide organ protection in management of hypertension. Clinical utility of these novel agents can be expanded owing to their more beneficial effects than the classical L-types of calcium channel blockers [7].

Cilnidipine

Cilnidipine is a newly developed CCB that has dual L- and N- type of calcium channel blocking properties. The two-directional mechanism by which cilnidipine reduces the blood pressure rather than acting on a single direction to control hypertension makes it a novel drug. Abnormal sympathetic activity has been associated with many complications of hypertension, including heart failure, renal failure and stroke. It has potential to reduce cardiovascular events directly by reducing BP through vasodilatation and indirectly by regulating the sympathetic system [8].

Researchers have extensively studied cilnidipine in its preclinical and clinical development phases. Both in animal examinations and in clinical practice, cilnidipine have shown promising renoprotective, neuroprotective and cardio protective effects. Besides its N-type of calcium channel blocking effects cilnidipine may have pleiotropic effects as observed in various research. This article tries to review the current understanding of the clinical utility and pharmacological profile of cilnidipine as a unique antihypertensive agent. Since except for cilnidipine other dihydropyridine CCBs lacks the anti-sympathetic activity, cilnidipine can be categorized as a new generation (4^{th}) owing to its effects on sympathetic function.

N-type Calcium channel blocking effect

N- Type of calcium channels is located at the nerve endings of the sympathetic and central nervous systems, where they regulate the release of neurotransmitters. About 85% of all Ca^{2+} currents in the

sympathetic neurons are contributed by N-type of Ca^{2+} channels.

Uneyama *et.al.*conducted comparative studies of various DHPs on their L-type of calcium channel blocking effects in isolated ventricular myocytes with their N-type of calcium channel blocking effects in isolated superior cervical ganglion neurons of wistar rats. At concentration of 1μM all DHPs except cilnidipine showed minimal inhibitory effect on N-type of Calcium channel. The tested compound showed marked difference in their channel selectivity. While nifedipine showed highest selectivity for L-type calcium channels, cilnidipine showed significant selectivity for both L-type and N-type of calcium channel. Study demonstrated that N-type Ca channel currents in isolated sympathetic neurons can be effectively suppressed by sub-micro molecular concentrations of cilnidipine [9].

N-type of calcium channel blocking action of cilnidipine was confirmed in IMR32 human neuroblastoma cells by Takahara. A. *et al* [10]. Several invitro studies by Nap. A. *et al*. demonstrated that release of norepinephrine from sympathetic nerve ending is attenuated by cilnidipine [11]. In vivo experiments using anesthetized rats [12] and dogs [13] have confirmed this observation.

Cardioprotective effect

The cardiovascular selectivity of various Ca^{2+} channel blockers were analyzed quantitatively using blood-perfused canine heart model. Cilnidipine has been demonstrated higher vascular selectivity and about ten times more potent coronary vasodilatory action than nicardipine [14].

Cardio protective action of cilnidipine has been demonstrated in rabbit based myocardial ischemia model, where during the phase of ischemia and in the reperfusion period, cilnidipine reduces the level of norepinephrine in myocardial interstitium. Cilnidipine not only reduces the infract size but also reduced the post infract incidence of ventricular premature beats [15]. In model of vasopressin-induced angina in rat, cilnidipine showed anti anginal effects [16] and in canine model of long QT syndrome, improvement in ventricular repolarization has been seen [17].

Both in vivo and in vitro studies and also clinical studies sympatholytic profiles of cilnidipine have been observed [8, 11].

A comparative study of 24 hours ambulatory blood pressure control in hypertensive patients in 2005 by Hoshideet.al; has shown that in the cilnidipine group there was significantly greater reduction in heart rate than amlodipine group [18].

In a multi centric study in Japan by Nagahama S *et al*.; among 2920 patients of sever hypertension, cilnidipine was added to angiotensin receptor blocker monotherapy. Patients who were having a higher baseline heart rate ≥75 beats/min showed significant reduction of basal heart rate and reached the desired goal of blood pressure and very few central nervous system related side effect were noted [19].

"White-coat hypertension" and "Morning hypertension" are closely related with sudden sympathetic nervous system activation. Cilnidipine has clinically demonstrated effectiveness in both this condition [20, 21].

Improvement of Left ventricular function by cilnidipine has been seen in CANDLE trial and other clinical studies. 72 patients with uncomplicated hypertension were studied by Chung and associates. This patient received either atenolol or cilnidipine for 36 weeks. The cilnidipine-treated arm showed a reduced left atrial volume, while increase left atrial volume was seen in the atenolol-treated arm. In the management of essential hypertension with left ventricular diastolic dysfunction the left atrial size reduction effect of cilnidipine may prove beneficial [22, 23].

In the Dahl salt-sensitive hypertensive rat model, cardiac remodeling and diastolic dysfunction was attenuated by cilnidipine to a greater extent than amlodipine [24].

Renoprotective effects

Progression of kidney disease has close association with glomerular hypertension. In hypertensive patients it is important to keep glomerular pressure lower by dilation of both afferent and efferent arteries. Ca^{2+} channel blockers have variable sensitivity to afferent and efferent arteries, therefore appropriate Ca^{2+} channel blockers should be selected for hypertensive patients with chronic kidney disease. Both afferent and efferent arterioles have sympathetic innervation; hence N-type Ca^{2+} channel activity to some extent implicated in regulation of the glomerular pressure.

In vitro isolated perfused hydronephrotic kidney cilnidipine elicits predominant action on afferent arterioles. Cilnidipine has dilated both afferent and efferent arterioles in hydronephrotic kidney of anesthetized rats. Inhibition of renal N-type of Ca^{2+} channel will dilate both afferent and efferent arterioles by suppressing the release of norepinephrine. Cilnidipine reduces plasma norepinephrine level in renal injury animal models and reduces the glomerular capillary pressure, afferent and efferent arteriolar resistances and consequently reduces urinary albumin excretion [25].

In the multiple risk factor intervention trial (MRFIT), strong relation between high blood pressure and end stage renal disease has been established [26]. Proteinuria, albuminuria and chronic renal dysfunction are itself independent risk factor of cerebrovascular and cardiovascular diseases. Hence strategies of hypertension management should also focus on efforts to reduce the development of renal disease and to decrease the risk of vascular events. In a clinical study by Rose and Ikebukoro, in hypertensive patients with benign nephrosclerosis, cilnidipine showed equal effectiveness in reducing urinary albumin excretion in, as benazepril, an angiotensin converting enzyme inhibitor [27].

Greater renoprotective action of cilnidipine in comparison to conventional L-type of Ca^{2+} channel blockers has been demonstrated in studies conducted by Tsuchihasi T *et al* [28]. Combination of cilnidipine with valsartan showed greater reduction in the albumin/creatinine ratio than valsartan alone in a study by Katayama. K. *et al* [29].

A multi-centric open level study, cilnidipine versus amlodipine randomized trial for evaluation in renal disease (CARTER) demonstrated in combination with angiotensin receptor blocker cilnidipine is superior to amlodipine, in preventing the progression of proteinuria in patients with hypertension and chronic renal disease [30]. Low-grade albuminuria in hypertensive CKD patients is safely and effectively reduced by cilnidipine [31].

Cardiovascular disease and related mortality has been closely associated with renal function thus renoprotective effect of cilnidipine may contribute to cardio protection.

Neuroprotective effects

Auto regulatory function of cerebral blood vessels allows a constant cerebral blood flow even in the setting of abrupt blood pressure changes. This auto regulatory mechanism fails at certain extent leading to cerebrovascular accidents. Activation of N-type of Ca^{2+} channels are implicated in the pathophysiological processes that induces cerebral ischemia.

Cerebral blood flow is maintained in spite of blood pressure lowering effect of cilnidipine and at the same time the lower limit of cerebral autoregulation shows a downward shift. The size of cerebral infracts shows reduction in size at usual antihypertensive dose of cilnidipine [32].

Level of ß-thromboglobulin, (a marker of platelet activation), has been increased in association with increased sympathetic tone. It has been implicated in formation of cerebral arterial thrombosis. Cilnidipine has shown to decrease the level of ß-thromboglobulin in a clinical study of cold pressor test, may provide protection from cerebral arterial thrombosis [33].

Metabolic effect

Metabolic syndrome is associated with central obesity, insulin resistance, dyslipidemia and hypertension. In association with increasing body weight there is increased sympathetic activity. In metabolic syndrome it is important to control sympathetic over activity. Secretion of Insulin from β-cells and secretion of glucagon from α-cells in the islets of Langerhans of pancreas are both Ca dependent process. Sympathetic activity influence the secretion of both this hormones and therefore N-type of Ca^{2+} channels play important role in glucose homeostasis.

In hypertensive patients with type 2 diabetes mellitus, cilnidipine reduced 24 hrs urinary catecholamines which in long run may help in improving insulin resistance (34). By homeostasis model assessment (HOMA-R) method, in obese patient lowering of fasting serum immunoreactive insulin (F-IRI) and insulin resistance index is seen after treatment with cilnidipine. There is also notable increase in level of dehydroepiandrosterone (DHEA) and serum DHEA-sulfate (DHEA-S). [35]

Cilnidipine improves glucose tolerance and insulin sensitivity without affecting the adiposity or body weight of obese mice. [36]

Clinical study in patients of hypertension and Type II diabetes mellitus, by Masudsa et.al.in 2011, demonstrated the beneficial effect of cilnidipine on glucose and lipid metabolism and renal function. [37]

White adipose tissues expresses N-type calcium channel. In obese patients with, hypertensive cerebrovascular disorder cilnidipine lowered the plasma leptin levels. Cilnidipine along with controlling blood pressure, also prevent leptin induced atherosclerosis in obese hypertensives and can thus reduce the risk of cerebrovascular accident [38].

By virtue of its effects cilnidipine can be a useful therapeutic tool in management of metabolic syndrome.

Other Benefits

Study by Fan *et al* in 2011, indicates cilnidipine can relaxes human internal thoracic artery by enhancing the production of nitric oxide by endothelial nitric oxide synthase (eNOS) and blocking Ca^{2+} channels at the same time [39].

In 2013, RanjanShetty, G Viveket.al, in a study on 27 patients of essential hypertension with amlodipine induced ankle edema, successfully substituted amlodipine to cilnidipine as an effective alternative [40].

A meta-analysis of the efficacy and safety of cilnidipine in Chinese patients with mild to moderate essential hypertension was conducted by XuGuo-Ling *et al*. in 2012 conclude cilnidipine as a useful agent for mild to moderate hypertension [41].

CONCLUSION

Cilnidipine have a dual L/N-type calcium channel blocking property and has an important role in management of hypertension and prevention of its associated systemic complications. Effective suppression of neurohumoral regulation of cardiovascular system by means of inhibition sympathetic nervous system over activity and modulation of the renin-angiotensin-aldosterone system can be achieved successfully by cilnidipine therapy**.** N-type of Ca^{2+} channels play important role in glucose homeostasis and therefore cilnidipine may be a useful therapeutic tool in management of metabolic syndrome. Thus it is expected to be beneficial in prevention of various complications arising due to high blood pressure. It can be used effectively in combination with other antihypertensive agents for refractory cases.

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