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A Prospective Interventional Study on Clinical Effects of Cilnidipine in Hypertensive Patients

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Abstract: Aim: The aim of the present study was to evaluate the clinical effects of Cilnidipine on sympathetic nervous system, blood pressure, heart rate, renal function and lipid profile in hypertensive patients.
Methods: A prospective interventional study was conducted in a total 45 hypertensive patients using other calcium channel blockers for more than 2 months. They underwent a drug free period of 7 days and a treatment period with Cilnidipine for 8 weeks. Sympathetic function tests and blood glucose test, lipid profile test, serum creatinine and Albumin Creatinine Ratio were performed at the baseline and 8 weeks after completion of Cilnidipine treatment.
Results : Cilnidipine is effective in reducing heart rate and blood pressure when compared to baseline values. Sympathetic function tests showed significant improvement after Cilnidipine treatment. ACR and serum creatinine levels have decreased significantly from the baseline values showing renoprotective effect of Cilnidipine. Blood glucose levels did not significantly change when compared to baseline levels except in diabetic patients with hypertension. Lipid profile does not show significant change from the baseline values except for the triglycerides in diabetic patients with hypertension.
Conclusion : Cilnidipine is an effective once-daily antihypertensive agent. As it inhibits both L- and N-type calcium channels, it will be useful for patients with hypertension and cardiovascular disease, sympathetic over activity, diabetes mellitus, dyslipidemia or renal disease and proves to be a better alternative to existing calcium channel blockers. Therefore, Cilnidipine can be selected as treatment option according to the pathophysiological condition of the patient.
Key words: Hypertension, Dyslipidemia, Diabetic, Cardiovascular disorders.

Introduction:

Cilnidipine is a unique fourth generation calcium channel blocker which has dual action by blocking both L-type calcium channels present on vasculature on smooth muscle and N-type calcium channels present on sympathetic nerve endings and inhibits excessive release of norepinephrine[1]. As hypertension is one of the major public health problems and there is an immense need to control the complications of hypertension, an anti-hypertensive agent which is beneficial in most of the pathophysiological complications of hypertension is required.

Strict blood pressure and blood glucose control is necessary to reduce the incidence of myocardial infarction, sudden death and cerebral infarction and the strict treatment with appropriate drugs has reduced their deaths[2]. CCBs are effective anti-hypertensive drugs. Despite their efficacy, they have certain drawbacks like reflex tachycardia, by which they are not suitable for certain patients with IHD and tachyarrhythmias[3]. This side effect is absent with Cilnidipine due to its N-type Calcium channel blocking property by controlling sympathetic over activity[4]. There are atleast six subtypes of calcium channels; namely , L-, N-, P-, Q-, R-, and T- type, based on electrophysiological and pharmacological evidence . Of late, unlike other CCB's the newer and unique 4th generation CCB, Cilnidipine, which works by blocking both N-type and L-type calcium channels, thus shows clinical advantages over other dihydropyridines, on heart rate, sympathetic nervous system, renal function, glucose and lipid metabolism other than controlling blood pressure[4,5,6]. It has slow onset and long lasting vasodilating effect[7].

Recent studies suggest that N-type calcium channel blocking property plays a key role in suppressing norepinephrine release from the nerve terminals, thus decreasing cardiovascular morbidity and mortality [8]. Sympathetic activation cause by rapid vasodilating action seen with other calcium channel blockers is absent with cilnidipine [9]. According to the latest guidelines JNC-VII, the goal of anti hypertensive therapy is to attain a blood pressure of <130/80 mmHg [6].

The study was undertaken to study the clinical efficacy of cilnidipine on blood pressure, heart rate, sympathetic nervous system function, renal function, glucose and lipid metabolism in patients with hypertension (and type 2 DM)

Materials and Methods:

Total 45 patients with mild to moderate essential hypertension receiving dihydropyridine calcium channel blockers except cilnidipine, as monotherapy for hypertension, at the outpatient department in Mahatma Gandhi Memorial Hospital, Warangal, Telangana, India were participated in the study. Out of 45 participants, 11 were diabetic.

Approval was obtained from the Hospital and Institutional Ethical committee prior to the start of the study. Informed consent was obtained from each patient in writing after being informed about the purposes of study and procedures to be followed during the study.

It is an open labelled, prospective interventional study design. A drug free period of 7 days was given to the patients and cilnidipine drug treatment was given for 8weeks. The goal of the blood pressure was set at ≤130/80 mmHg, and attempts were made to keep the blood pressure at this for 8 weeks or longer. During the study period, Cilnidipine was given as mono drug therapy to treat hypertension, no other CCB or other anti hypertensive drug was given. By adjusting the dose levels of cilnidipine, attempts were made to achieve the goal blood pressure.

All the parameters were tested at the baseline and 8 weeks after the cilnidipine treatment. The blood samples were taken after an overnight fasting at the baseline and after 8 weeks of treatment with cilnidipine. SBP, DBP and HR were measured with automated sphygmomanometer (OMRON; model HEM-7120). Sympathetic function tests including Postural hypotension test and isometric handgrip test were performed at baseline and after 8 weeks, using Cardiac Autonomic Neuropathy Analyser Model CANS 504 by Diabetik Foot Care India Pvt Ltd. Change in systolic blood pressure and change in diastolic blood pressure are observed in Postural hypotension test and Isometric handgrip test, respectively. Grades were given according to the changes in blood pressure in sympathetic function tests. Serum concentrations of lipid profile (Total cholesterol, LDL-C, HDL-C and Triglycerides), Urine Albumin Creatinine Ratio (ACR) were analyzed using kits from Proton company in CPC autoanalyzer instrument. Blood glucose levels (FBS and PLBS) were analyzed by GOD/POD method using calorimeter.

All parameters were expressed as mean values ± SD. Data analyses were performed using the GraphPad prism 5. A paired t-test was used to assess significant differences between values obtained before and 2 months after the change of drug treatment to cilnidipine. A P-value <0.05 was considered statistically significant.

Results:

All the 45 patients completed the 8 weeks study period with cilnidipine. Table:2 summarises the characteristics of the participants of the study at baseline and after treatment with cilnidipine.

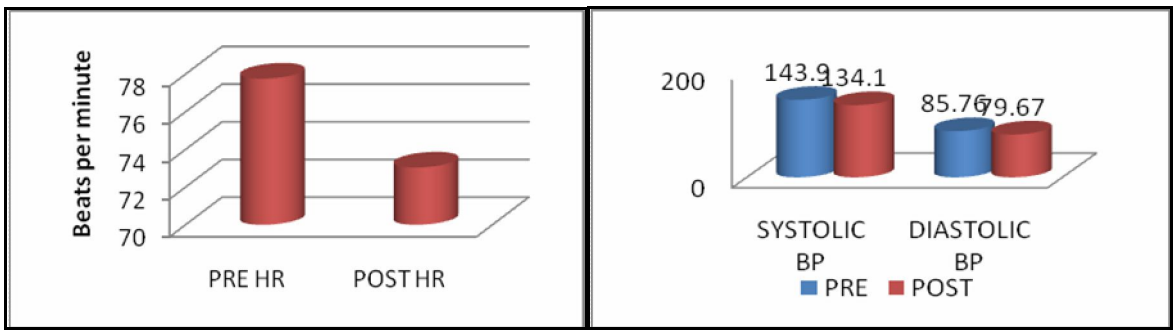


Figure 1: Effects of Cilnidipine on heart rate and blood pressure after treatment.
PRE HR: Pre heart rate, POST HR: Post heart rate

Postural hypotension test and isometric handgrip test were performed under sympathetic function tests. In postural hyotension test number of patients with grade 0, grade 1 and grade 2 were 14, 25 and 6 respectively at the baseline. 2 months after switching to cilnidipine there were 26, 18 and 1 patients with grade 0, grade 1 and grade 2 respectively.In isometric handgrip test number of patients with grade 0, grade 1 and grade 2 were 3, 13 and 29 patients respectively. 2 months after switching to cilnidipine there were 13, 17 and 15 patients with grade 0, grade 1 and grade 2 respectively.

Figure 2: Effect of Cilnidipine on change in systolic Blood pressure in Postural Hypotension Test and Change in Diastolic blood pressure in Isometric Handgrip Test after treatment.

Figure 2: Effect of Cilnidipine on change in systolic Blood pressure in Postural Hypotension Test and Change in Diastolic blood pressure in Isometric Handgrip Test after treatment.

After 8 weeks of treatment with cilnidipine, the change in ACR was very significant, change in the serum creatinine was significant (p=0.001).

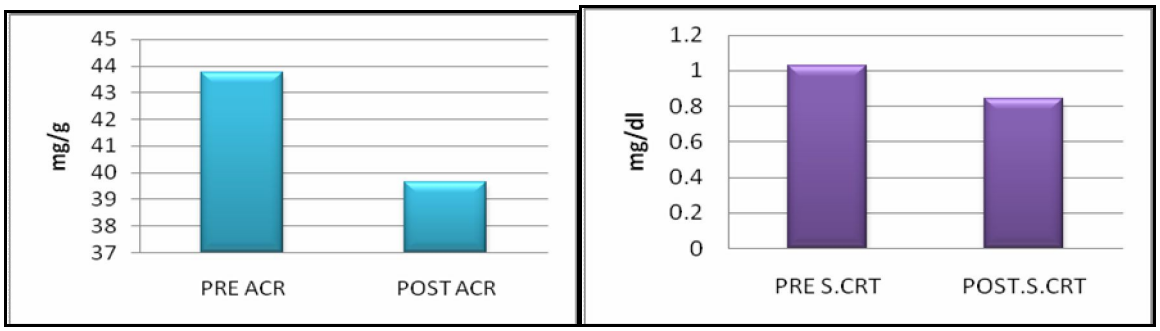


Figure 3: Effect of Cilnidipine on ACR and Serum creatinine indicating renal function after treatment.
ACR: Albumin Creatinine Ratio, S. CRT: serum creatinine

The change in blood sugar levels in overall population was not significant. But in diabetic patients the decrease of FBS and PLBS was significant after switching to cilnidipine treatment.

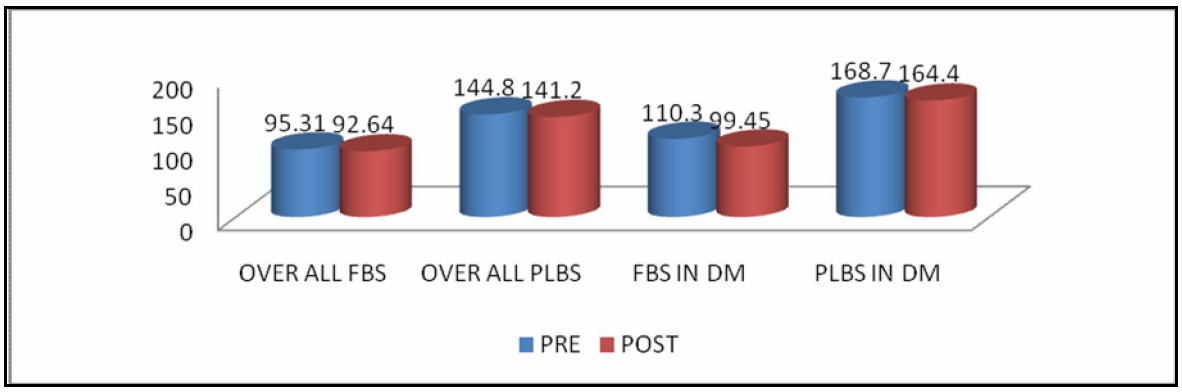
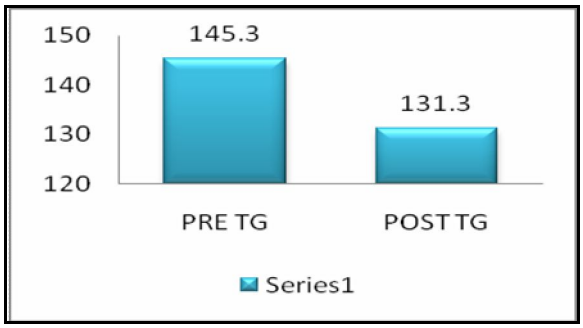


Figure 4 : Comparison of change in blood sugar levels in diabetic and non diabetic hypertensive patients

There were no significant differences between the baseline and cilnidipine treatment in terms total cholesterol, HDL-C, LDL-C level and TG. But, when diabetic patients are concerned, triglycerides alone have decreased significantly after switching to cilnidipine treatment. HDL-C, LDL-C and total cholesterol levels did not improve significantly even in diabetic patients.



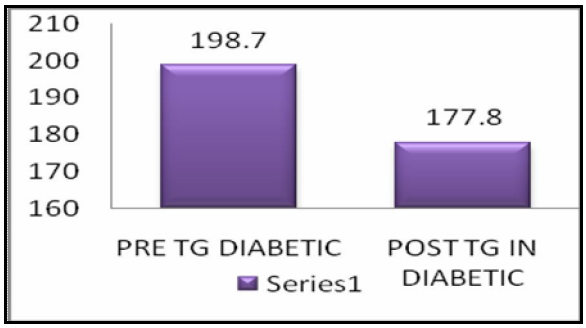


Figure 5: Change in triglycerides

Figure 6: change in TG in diabetic

Discussion:

A unique 4th generation calcium channel blocker Cilnidipine, that inhibits multiple calcium channels have been developed over the past decade. Treatment of hypertension is carried out by different types of calcium channel blockers such as long acting and short acting CCB's and also on the basis of different sub types of calcium channels they block. All the 3 generation calcium channels acts significantly only on L-type calcium channels, expressed on vascular smooth muscle [11]; but cilnidipine acts significantly both on N-type calcium channels located on peripheral sympathetic nerve fibers and L-type calcium channels located on vasculature [12]. Therefore, we observed the effect of cilnidipine on hypertensive patients using a prospective interventional study design. Recent studies have reported a higher heart rate is associated with a long term risk of cardiovascular mortality, independent of other cardiac risk factors[13,14]. Treatment with short acting CCB's may not prevent cardiovascular mortality[15,16]. Therefore, slow onset and long acting calcium channel blocker which exert less influence on the sympathetic nervous system activation is preferred for the treatment of hypertension[17].

In the present study, switching from other calcium channel blockers to cilnidipine had significantly decreased blood pressure and heart rate. This is reliably explained by the inhibitory action of cilnidipine on cardiac sympathetic nervous activity[18]. The main side effects of short acting CCB's is reflex tachycardia; replacing these drugs with long acting Cilnidipine has shown decrease in heart rate, leading to a reduction in the mortality of hypertensive patients.

As increased sympathetic nervous system activity increases blood pressure and contributes to the development and maintenance of hypertension through stimulation of the heart, peripheral vasculature, and kidneys, causing increased cardiac output, increased vascular resistance, and fluid retention, controlling its activity is important to reduce the morbidity associated with it[19]. In addition, autonomic imbalance (increased sympathetic tone accompanied by reduced parasympathetic tone) has been associated with many metabolic, hemodynamic, trophic, and rheologic abnormalities that result in increased cardiovascular morbidity and mortality [20]. Furthermore, since diastolic blood pressure relates more closely to vascular resistance than to cardiac function, these results also suggest that increased sympathetic tone may increase diastolic blood pressure by causing vascular smooth-muscle cell proliferation and vascular remodeling [21]. In the present study we observed a significant improvement in Sympathetic Nervous System from postural hypotension test and isometric handgrip test after switching to cilnidipine treatment for 8 weeks. Thus, supporting the evidence of sympathetic suppression through blocking of N-type calcium channels.

It is essential to suppress the onset and progression of renal dysfunction in patients with hypertension and diabetes mellitus. secretion of renin from the juxtaglomerular apparatus is closely associated with renal sympathetic nerve activity. Cilnidipine suppresses renin-angiotensin system through blockade of N-type calcium channels on sympathetic nerves present on kidney[22]. Cilnidipine also decreased the plasma concentration of aldosterone level according to a study which has clearly demonstrated that the endocrine mechanisms of angiotensin II- induced aldosterone production in the adrenocortical cells are closely associated with activities of N-type $Ca2^{+}$ channels. As the renal nerve stimulation releases norepinephrine and induces renal vasoconstriction through activation of adrenoceptors in the vascular vessels, typical L-type Ca^{2+} channel blockers cannot suppress this action [22]. Glomerular filtration is essentially regulated by afferent and efferent arterial tone . Since sympathetic nerves are distributed in the afferent and efferent arteries, N-type Ca^{2+} channel blocking activity may partly control the glomerular pressure. According to a study in which hydronephrotic kidney model of the rat was used, Cilnidipine has been demonstrated to dilate both afferent and efferent arteries [23].

All these effects of cilnidipine in renoprotection has been supported by the results from the present study. A significant reduction in urinary ACR was observed in the present study after cilnidipine treatment. According to hypertension guidelines for the management of hypertension, albuminuria should be reduced to <30mg/g creatinine in diabetic patients. In the present study, 11 (24.4%) and 18 (40%) patients has achieved this target at the baseline and after cilnidipine treatment, respectively. Albuminuria has been established as an independent risk factor for cardiovascular events; increase in albuminuria elevates the risk and decrease in albuminuria reduces the risk of developing such events[24,25]. A significant reduction in serum creatinine levels was also observed in the present study, owing to renoprotective effects of cilnidipine. Concerning glucose metabolism, in a study using N-type Ca^{2+} channels α_{1B} subunit homozygous knockout mice fed normal diet, improved glucose tolerance was observed without any change in insulin sensitivity [26]. In another study with fructose-fed rats, insulin resistance improved significantly after cilnidipine treatment [27]. pancreatic insulin secretion from β-cells and glucagon secretion from α-cells in the islets of langerhans are Ca^{2+} dependent processes, probably initiated by influx of Ca^{2+} through N-type Ca^{2+} channels [22]. The results from the present study shows that fasting blood glucose and post lunch blood glucose are lowered significantly from the baseline values in diabetic group, but not overall study subjects; indicating that N-type Ca^{2+} channels play a significant role in glucose homeostatsis mostly in diabetic patients with hypertension. When lipid metabolism is concerned, overall significant decrease in total cholesterol, LDL-C, HDL-C and triglycerides was not observed in the present study, but triglycerides alone have decreased significantly in diabetic patients with hypertension, supporting the results from the previous study[28,29]. This results indicate that, cilnidipine shows protective effects against atherosclerosis and the risk of heart disease and stroke mostly in diabetic patients. Table 3 summarises the significance of glucose and lipid profile in diabetic patients with hypertension.

Table 1: Grades in sympathetic function tests:

Test	Grade-0 (Normal)	Grade-1 (Border line)	Grade-2 (Abnormal)
Postural hypotension test	<10 mmHg	11 ~ 29 mmHg	>30 mmHg
Isometric handgrip test	>16 mmHg	11 ~ 15 mmHg	<10 mmHg

Table 2: Effect of drug

Parameter	Baseline	Cilnidipine	P-Value
Blood pressure: Systolic BP (mmHg) Diastolic BP (mmHg)	 143.9±15.40 85.76±9.0	 134.1±14.42 79.67±8.744	 0.002 0.0016
Heart rate (beats/min)	77.76±12.18	73.04±10.59	0.0002
Sympathetic function tests: -postural hypotension test: change in systolic BP (mmHg) -isometric handgrip test: change in diastolic BP (mmHg)	 13.07±8.37 8.489±5.574	 8.95±6.7 13.64±5.717	 <0.0001 <0.0001
Renal function: -ACR (mg/g) -serum creatinine (mg/dl)	 43.76±15.90 1.027±0.345	 39.64±14.65 0.842±0.186	 <0.0001 0.001
Blood sugar: -FBS (mg/dl) -PLBS (mg/dl)	 95.31±24.24 144.8±29.79	 92.64±17.54 141.2±25.79	 0.09 0.139
Lipid profile: Total cholesterol (mg/dl) -HDL-C (mg/dl) -LDL-C (mg/dl) -TG (mg/dl)	 168.4±35.97 44.53±11.41 116.1±33.09 145.3±71.16	 160.9±29.22 47.37±10.23 111.4±28.12 131.3±62.04	 0.061 0.052 0.074 0.093

Table 3:Blood sugar and lipid profile in diabetic group (n=11)

Parameter	Baseline	Cilnidipine	P-Value
Blood sugar: -FBS (mg/dl) -PLBS (mg/dl)	 110.3±39.33 168.7±41.59	 99.45±28.14 164.4±38.33	 0.034 0.034
Lipid profile: -total cholesterol (mg/dl) -HDL-C (mg/dl) -LDL-C (mg/dl) -TG (mg/dl)	 185.0±36.75 43.45±14.01 115.8±41.27 198.7±90.21	 179.1±32.33 49.43±10.51 110.0±34.68 177.8±87.05	 0.093 0.135 0.066 0.046

References:

1. Takahara A. Cilnidipine: A new generation Ca^{2+} channel blocker with inhibitory action on sympathetic neurotransmitter release. Cardiovasc. Ther., 2009, 27; 124-139.
2. Adler AI, Stratton IM. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. BMJ., 2000,321; 412–419.
3. Satoshi HOSHIDE, Kazuomi KARIO. Comparison of the Effects of Cilnidipine and Amlodipine on Ambulatory Blood Pressure. Hypertens Res., 2005; 28, 12; 1003-1008.
4. Junichi Minami, Yuhei Kawano. Effects of cilnidipine, a novel dihydropyridine calcium antagonist, on autonomic function, ambulatory blood pressure and heart rate in patients with essential hypertension. J Clin Pharmacol., 2000, 50; 615-620.
5. M TANAKA: The L/N-Type Calcium Channel Blocker, Cilnidipine, Reduces Heart Rate and Albuminuria in Patients with Type 2 Diabetes. J Int MedRes., 2010, 38; 602-610.
6. Takashi Masuda, Misao N. 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. Cardiovascular Therapeutics., 2011, 29; 46–53.

7. Yoshimoto R, Dohmoto H. Prolonged inhibition of vascular contraction and calcium influx by the novel 1,4-dihydropyridine calcium antagonist cinaldipine. Jpn J Pharmacol., 1991, 56; 225-229.
8. Nap A, Mathy MJ. The evaluation of the N-type channel blocking properties of cilnidipine and other voltage-dependent calcium antagonists. Fundam Clin Pharmacol., 2004, 18; 309–319.
9. Lindqvist M, Kahan T. Long-term calcium antagonist treatment of human hypertension with mibefradil or amlodipine increases sympathetic nerve activity. J Hypertens., 2007, 25; 169–175.
10. Angus JA, Wright CE. Targetting voltage-gated calcium channels in cardiovascular therapy. Lancet., 2000, 356; 1287–1289.
11. Hirning LD, Fox AP. Dominant role of N-type Ca2+ channels in evoked release of norepinephrine from sympathetic neurons. Science., 1988, 239; 57–61.
12. Zaki A. Zaman, Vishnu Kumari. Comparison of the effects of amlodipine and cilnidipine on blood pressure, heart rate, proteinuria and lipid profile in hypertensive patients. Int J Basic Clin Pharmacol., 2013 Apr, 2(2); 160-164
13. Gillman MW, Kannel WB. Influence of heart rate on mortality among person with hypertension: the Framingham Study. Am Heart J., 1993, 125; 1148-54.
14. Furberg CD, Psaty BM . Nifedipine: dose-related increase in mortality in patients with coronary heart disease. Circulation., 1995, 92; 1326-31.
15. Psaty BM, Heckbert SR. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA., 1995, 274, 620-625.
16. Chobanian AV, Bakris GL. The seventh report of the Joint National Committee on prevention,detection,evaluation and treatment of high Blood Pressure: the JNCI report. JAMA., 2003, 289., 2560-71.
17. Sakata K, Shirotani M. Effects of amlodipine and cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. Hypertension., 1999, 33, 1447 – 1452.
18. Mark AL. The sympathetic nervous system in hypertension: a potential longterm regulator of arterial pressure. J Hypertens Suppl., 1996, 14, 159-65.
19. Brook RD, Julius S. Autonomic imbalance, hypertension, and cardiovascular risk. Am J Hypertens., 2000, 13, 112-122.
20. Suzanne Oparil.MD, Amin Zaman. MD. Pathogenesis of Hypertension. Ann Intern Med., 2003, 139, 761-776.
21. Konda. T, Enomoto. A. Different effects of L/N-type and L-type calcium channel blockers on the renin angiotensin-aldosterone system in SHR/Izm. American Journal of Nephrology., 2009, 30, 2; 155-161.
22. Aritomi. S,Wagatsuma. H. Expression of N-type calcium channels in human adrenocortical cells and their contribution to corticosteroid synthesis. Hypertension Research., 2011, 34, 2; 193-201.
23. Konno. Y, Kimura. K. Vasodilatory effect of cilnidipine, an L-type and N-type calcium channel blocker, on rat kidney glomerular arterioles. International Heart Journal., 2008, 49, 6; 723-732.
24. Yuyun MF, Kannel WB. A prospective study of microalbuminuria and incident coronary heart disease and its prognostic significance in a British population: the EPIC-Norfolk study. Am J Epidemiol., 2004, 159; 284 – 293.
25. Alder AI, Stevens RJ. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int., 2003, 63; 225 – 232.
26. Takahashi. E, Ito. M. Increased glucose tolerance in N-type Ca2+ channel 1B-subunit gene-deficient mice. International Journal of Molecular Medicine., June 2005, 15, 6; 937–944.
27. Takada. M, Ura. N. Effects of cilnidipine on muscle fiber composition, capillary density and muscle blood flow in fructose-fed rats. Hypertension Research., 2001, 24, 5; 565-572.
28. Masuda T, Ogura MN. 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. Cardiovasc Ther., 2011, 29; 46-53.
29. Ahaneku JE, Sakata K. Effects of Cilnidipine on lipids, lipoproteins and fibrinolytic system in hypertensive patients. Drugs Exp Clin Res., 2000, 26; 119-123.

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