ORIGINAL ARTICLE

Comparison of amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in mild to moderate hypertensive individuals: A prospective study

Prabhakar Adake, Somashekar H.S.[1], Mohammed Rafeeq P. K., Dilshad Umar[2], Bahija Basheer[2], Kusai Baroudi[2]

Department of Pharmacology, Yenepoya Medical College, Yenepoya University, Mangalore, [1]Department of Pharmacology, Oxford Medical College, Bangaluru, Karnataka, India, [2]Department of Restorative Sciences, Al Farabi College, Riyadh, Saudi Arabia

J. Adv. Pharm. Technol. Res.

ABSTRACT

To compare amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in hypertensive individuals. This was a three months prospective, observational study done at the tertiary care center of Karnataka, India. A total number of 60 (n = 60) newly diagnosed hypertensives (≥140/90) of either gender, attending outpatient department of medicine, were included in the study. Out of 60 patients, 30 patients who have been prescribed tablet amlodipine 5–10 mg/day and the other 30 who have been prescribed tablet cilnidipine 10–20 mg/day orally by the consulting physician, depending upon the severity of hypertension were followed every fortnight, screened for the presence of pedal edema and blood pressure control over a period of 3 months. Antihypertensive efficacy between two groups was compared by unpaired t-test and incidence of pedal edema was compared by Fisher's exact test. Of 30 patients in the amlodipine group, 19 patients presented with pedal edema (63.3%) and 2 patients (6.66%) in cilnidipine group presented with pedal edema during the study period. There was a significant difference in the incidence of pedal edema between amlodipine and cilnidipine group ($P < 0.05$), but no significant difference was found in the antihypertensive efficacy of amlodipine and cilnidipine ($P > 0.05$). Both amlodipine and cilnidipine have shown equal efficacy in reducing blood pressure in hypertensive individuals. But cilnidipine being N-type and L-type calcium channel blocker, associated with lower incidence of pedal edema compared to only L-type channel blocked by amlodipine.

Key words: Blood pressure, calcium channel blockers, N-type and T-type calcium channels

INTRODUCTION

Hypertension is the most common cardiovascular disease. Around 50 million individuals in the United States and 1 billion individuals worldwide are affected by hypertension.[1] The prevalence varies in different populations and ethnic group.[2,3] In India, 29.8% population are suffering from hypertension.[4] Although there is dramatic age-related increase in the prevalence of hypertension, several important cardiovascular risk factors, particularly obesity, nutrient intake, physical activity, and diabetes also relate to the likelihood of hypertension. The Framingham heart study has estimated that individuals normotensive at the age of 55 years have a 90% lifetime risk of developing hypertension.[5] Hypertension represents a potent risk factor for cardiovascular, peripheral vascular, and renal diseases.[6-10]

The definition of hypertension as released by the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) is systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mm Hg, which simplifies hypertension classification by including only

Address for correspondence:
Dr. Prabhakar Adake,
Assistant Professor, Department of Pharmacology, Yenepoya Medical College, Yenepoya University, Mangalore - 575 018, Karnataka, India.
E-mail: dradake82@gmail.com

Access this article online

Quick Response Code:

Website: www.japtr.org

DOI: 10.4103/2231-4040.154543

stage I (SBP 140–159 mm Hg or DBP 90–99) or stage II (SBP 160 mm Hg or higher or DBP 100 mm Hg or higher). Perhaps the most important change is the new classification of "pre-hypertension" (SBP 120–139 mm Hg or DBP 80–89 mm Hg), which combines the normal and high normal categories of the previous JNC VI report, in the recognition of the fact that even these levels of BP confer an increased risk of the development of hypertension and future cardiovascular events.[11,12]

Drugs that lower blood pressure act by reducing peripheral resistance or cardiac output or both. Current pharmacological therapy for hypertension include diuretics (Thiazides, loop and K^+ sparing diuretics), sympatholytic drugs (α, β-antagonists), calcium channel blockers (CCBs) (nifedipine, amlodipine, cilnidipine), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and vasodilators. The choice of drug depends on the severity of hypertension and associated patient factors.

According to the European Society of Hypertension–European Society of Cardiology guidelines, all major classes of antihypertensive (Diuretics, β-blockers, CCBs, ACEIs, ARBs) are suitable for initial and maintenance therapy, either alone or in combination. High-risk conditions benefited by the use of CCBs include coronary artery disease and diabetes (particularly in combination with other agents). In addition, CCBs may be particularly useful in patients with co-morbid Raynaud's syndrome. Advanced age, isolated systolic hypertension, angina pectoris, peripheral vascular disease, carotid atherosclerosis, pregnancy are the conditions that favor the choice of a dihydropyridine (DHP) CCB.[13] Recently, in eighth JNC report, CCBs have shown good results over ACEI in the black population suffering from hypertension in terms of efficacy and prevention of stroke.[14]

Among the DHP CCBs, amlodipine has an outstanding pharmacokinetic and pharmacodynamic profile. The only major drawback of amlodipine is its adverse effect of peripheral edema. Incidence of peripheral edema with amlodipine has been found to be between 1.7% and 32% in different clinical studies.[15] Almost 9.3% of patients discontinue amlodipine therapy due to the adverse effects most commonly pedal edema.[16] The most serious consequence of amlodipine induced edema is discontinuation of the effective antihypertensive therapy. Edema may result in the need for dose reduction or drug withdrawal, either of which can adversely affect the efficacy. A new generation of CCB, cilnidipine is an N-type and L-type CCB that also inhibits sympathomimetic activity in contrast to other DHP. Although L-type and N-type DHP CCBs are being used clinically, their specific effects on the pedal edema have not yet been elucidated. Hence, this study was taken to compare the antihypertensive efficacy and incidence of pedal edema with amlodipine and cilnidipine in hypertensive individuals.

SUBJECTS AND METHODS

A 3 months prospective, observational study conducted at the Tertiary Care Centre of Karnataka, India between November 2010 and June 2011. The study protocol was confirmed to the ethical guidelines of Declaration of Helsinki (Sixth revision, 2008). Approval of the Institutional Ethics Committee and patient consent were obtained prior to the study.

Inclusion criteria

Newly diagnosed as hypertensives (BP ≥ 140/90) of either gender in the age group of 35–75 years, attending outpatient department of medicine.

Exclusion criteria

Patients with preexisting edema, corpulmonale, nephrotic syndrome, hypoproteinemia, anemia, pregnant women and who are on drugs such as nonsteroidal anti-inflammatory drugs and amantadine.

Study procedure

A total 60 patients (n = 60) who met the inclusion criteria were recruited in the study. The patients were examined by the consultant physician and blood pressure was measured in right arm, sitting posture by the auscultatory method using standard mercury sphygmomanometer. Two recordings of blood pressure were taken at an interval of 15–20 min by the same consultant. Pedal edema was assessed by clinical method over the medial malleolus of both legs. Presence of pedal edema on either of the legs is considered as positive for the pedal edema.

After initial screening, demographic data, past medical history, family history, and findings of clinical examination were recorded in the case report form. Of 60 patients, 30 patients who have been prescribed tablet amlodipine 5–10 mg/day and other 30 who have been prescribed tablet cilnidipine 10–20 mg/day orally by the consulting physician depending upon severity of hypertension, were included in this study. Patients were instructed to take the prescribed anti-hypertensive medication as per physician's advice. Patient compliance was assessed by pill count method on every visit. All the 60 patients were followed every fortnight, screened for pedal edema and blood pressure control over a period of 3 months. Patients were instructed to consult the physician immediately in case of any unusual side effects (including pedal edema) if it occurs before the follow-up date.

RESULTS

All the 60 patients completed the study. Patient's age for both the groups ranged between 30 and 75 years, with the

mean age being 59.8 ± 9.7 years in the amlodipine group and 50.0 ± 9.8 years in cilnidipine group [Table 1]. Women (n = 17) were more than men (n = 13) in both the study groups. Both the groups were comparable in all aspects.

There was a significant reduction in systolic and DBP ($P < 0.05$) in both groups compared to baseline data [Table 2]. However, there was no significant difference in the antihypertensive efficacy of both drugs ($P > 0.05$).

Of 30 patients in cilnidipine group 2 patients (6.66%) presented with edema within 2 weeks of therapy, whereas 19 patients (63.3%) presented with edema (within 2 weeks of therapy) in amlodipine group [Table 3 and Figure 1]. Cilnidipine has shown significant reduction in the incidence of pedal edema when compared to amlodipine ($P < 0.05$). There were no other significant adverse reactions observed in either amlodipine or cilnidipine group (other than pedal edema).

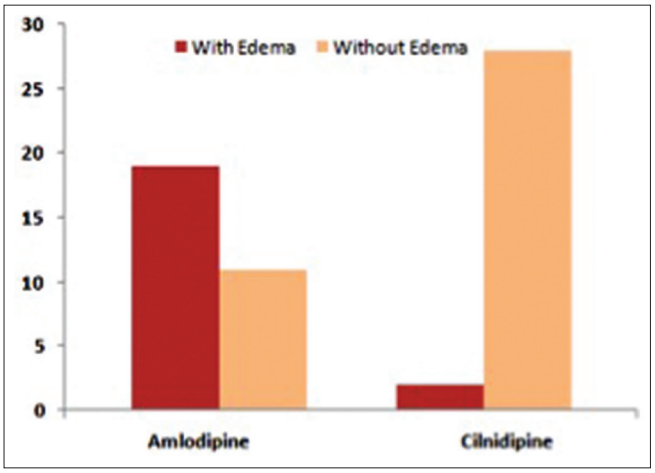

Figure 1: Bar diagram showing incidence of pedal edema in both the groups

Table 1: Demographic data of the patients

Patients	Amlodipine	Cilnidipine	Total
Number of patients	30	30	60
Age (years)			
Mean±SD	59.8±9.7	50.0±9.8	54.9±9.7
Range	40-75	35-72	35-75
Gender			
Male	13	13	26
Female	17	17	34

SD: Standard deviation

Statistical analysis

Antihypertensive efficacy between two groups was compared by unpaired t-test. The differences in the incidence of pedal edema between cilnidipine and amlodipine groups were compared by Fisher's exact test. A $P < 0.05$ was considered statistically significant.

DISCUSSION

Clinical effects of DHP CCBs such as blood pressure lowering effect are mainly related to its action on L-type calcium channels. In contrast to arterioles, venules seem not to respond to L-type CCB or agonist. This was proved by many studies which have shown that nifedipine could not dilate venules of striated muscle in spontaneously hypertensive rats, and L-type calcium channel agonist could not constrict venules of frog skin.[17] Despite similar blood pressure reduction, the frequency of pedal edema varies between CCBs. Hence, its occurrence cannot be explained by a difference in their influence on peripheral arteries.[18] Therefore, drugs that specifically inhibit L-type channels like nifedipine, reduce the blood pressure by dilating resistance arterioles, but not venules, so that the pressure in the afferent capillaries peripheral to the resistance arteries increases above the oncotic pressure and extravasation occurs. In fact, a decrease in the frequency of pedal edema due to L-type calcium blockers is reported when these drugs are combined with ACEI, which have a vasodilatory effect on the venules.[19]

N-type calcium channels are distributed in the neurons and have an important role in regulating sympathetic activity.[20] Sympathetic nerves are found in the venules, so drugs that block N-type calcium channels possibly cause venodilation.[21]

Cilnidipine is a 1,4- DHP CCB that suppresses the influx of calcium ions via L-type and N-type calcium channels, thus reducing the blood pressure through vascular smooth muscle relaxation and arterial dilatation.[22-24] It is used as an antihypertensive agent with a long duration of action that allows once-daily dosing.[25] Cilnidipine is known to suppress catecholamine release from peripheral sympathetic nerves as it blocks N-type channels in sympathetic nerve

Table 2: Comparison of antihypertensive efficacy of amlodipine with cilnidipine

BP	Treatment	PreRx BP	PostRx BP	Difference	t*	P**
SBP	Amlodipine	162.0±7.8	138.9±10.9	23.1±8.8	14.35	<0.001
	Cilnidipine	164.7±9.5	143.6±6.8	21.1±9.2	12.58	<0.001
	Amlodipine** versus cilnidipine	t=1.19 P=0.24, NS	t=2.01 P=0.04, S	t=0.89 P=0.38, NS	-	-
DBP	Amlodipine	91.9±8.8	79.5±7.0	12.5±9.6	7.07	<0.001
	Cilnidipine	93.7±7.6	83.3±6.0	10.3	8.60	<0.001
	Amlodipine** versus cilnidipine	t=0.81 P=0.42, NS	t=2.30 P=0.02, S	t=1.00 P=0.32, NS	-	-

*Paired t-test, S: Significant, NS: Not significant, **Unpaired t-test. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BP: Blood pressure

Table 3: Details of patients presenting with pedal edema in both groups

Data analyzed	Edema (%)*	Without edema (%)	Total
Amlodipine	19 (63.3)**	11 (36.7)	30
Cilnidipine	02 (6.66)**	28 (93.3)	30
Total	21 (35)	39 (65)	60

*Fisher's exact test, **$P<0.001$

terminals as well as having a common L-type calcium channel-blocking effect.[26] It has been shown that cilnidipine does not cause coronary sympathetic hypertonia in response to blood pressure reduction, unlike L-type channel blockers.[27] When administered to the patients with essential hypertension, cilnidipine suppressed cardiac sympathetic over activity and an increase of heart rate with blood pressure reduction.[28] Previous study has also shown that cilnidipine is well-tolerated by the hypertensive patients and associated with minor adverse effects such as headache, dizziness, cough, and gastrointestinal symptoms which are comparable to amlodipine.[29]

Accordingly, CCBs with an N-type channel blocking effect may dilate the venules through sympathetic nerves distributed to these vessels. Hence have a lesser incidence of pedal edema compared with the other CCBs which act only on L-type calcium channels.

CONCLUSION

Both amlodipine and cilnidipine have equal efficacy in reducing blood pressure in hypertensive individuals. But cilnidipine being N-type and L-type CCB, associated with lower incidence of pedal edema compared to only L-type channel blocked by amlodipine.

ACKNOWLEDGMENT

We are grateful to J.B. Chemicals and Pharmaceuticals Ltd, Mumbai, India for providing cilnidipine samples for the study.

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 2003;289:2560-72.
2. Ecological analysis of the association between mortality and major risk factors of cardiovascular disease. The World Health Organization MONICA Project. Int J Epidemiol 1994;23:505-16.
3. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, *et al*. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 2003;289:2363-9.
4. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, *et al*. Hypertension in India: A systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertens 2014;32:1170-7.
5. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, *et al*. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA 2002;287:1003-10.
6. Stafylas PC, Sarafidis PA. Carvedilol in hypertension treatment. Vasc Health Risk Manag 2008;4:23-30.
7. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: Effects on the cardiovascular system. Circulation 2007;116:85-97.
8. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, *et al*. Resistant hypertension: Diagnosis, evaluation, and treatment: A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008;117:e510-26.
9. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med 2003;139:761-76.
10. Owen AJ, Reid CM. Cardio classics revisited: Focus on the role of amlodipine. Integr Blood Press Control 2012;5:1-7.
11. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: A cohort study. Lancet 2001;358:1682-6.
12. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, *et al*. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001;345:1291-7.
13. Basile J. The role of existing and newer calcium channel blockers in the treatment of hypertension. J Clin Hypertens (Greenwich) 2004;6:621-29.
14. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
15. Patil PA, Kothekar MA. Development of safer molecules through chirality. Indian J Med Sci 2006;60:427-37.
16. Weir MR. Incidence of pedal edema formation with dihydropyridine calcium channel blockers: Issues and practical significance. J Clin Hypertens (Greenwich) 2003;5:330-5.
17. Messing M, Van Essen H, Smith TL, Smits JF, Struyker-Boudier HA. Microvascular actions of calcium channel antagonists. Eur J Pharmacol 1991;198:189-95.
18. Pedrinelli R, Dell'Omo G, Nuti M, Menegato A, Balbarini A, Mariani M. Heterogeneous effect of calcium antagonists on leg oedema: A comparison of amlodipine versus lercanidipine in hypertensive patients. J Hypertens 2003;21:1969-73.
19. Pedrinelli R, Dell'Omo G, Melillo E, Mariani M. Amlodipine, enalapril, and dependent leg edema in essential hypertension. Hypertension 2000;35:621-5.
20. Mori Y, Nishida M, Shimizu S, Ishii M, Yoshinaga T, Ino M, *et al*. Ca (2+) channel alpha (1B) subunit (Ca (V) 2.2) knockout mouse reveals a predominant role of N-type channels in the sympathetic regulation of the circulatory system. Trends Cardiovasc Med 2002;12:270-5.
21. Smyth L, Bobalova J, Ward SM, Keef KD, Mutafova-Yambolieva VN. Cotransmission from sympathetic vasoconstrictor neurons: Differences in guinea-pig mesenteric artery and vein. Auton Neurosci 2000;86:18-29.
22. Uneyama H, Uchida H, Konda T, Yoshimoto R. Cilnidipine: Preclinical profile and clinical evaluation. Cadiovasc Drug Rev 1999;17:341-57.
23. Uchida R, Yamazaki J, Kitamura K. Characterization of Ca2+ current inhibition by cilnidipine using a beta-subunit antisense oligonucleotide. Eur J Pharmacol 2003;466:53-62.
24. Takahara A, Fujita S, Moki K, Ono Y, Koganei H, Iwayama S, *et al*. Neuronal Ca2+ channel blocking action of an antihypertensive

drug, cilnidipine, in IMR-32 human neuroblastoma cells. Hypertens Res 2003;26:743-7.

25. Minami J, Kawano Y, Makino Y, Matsuoka H, Takishita S. Effects of cilnidipine, a novel dihydropyridine calcium antagonist, on autonomic function, ambulatory blood pressure and heart rate in patients with essential hypertension. Br J Clin Pharmacol 2000;50:615-20.
26. Hosono M, Fujii S, Hiruma T, Watanabe K, Hayashi Y, Ohnishi H, *et al.* Inhibitory effect of cilnidipine on vascular sympathetic neurotransmission and subsequent vasoconstriction in spontaneously hypertensive rats. Jpn J Pharmacol 1995;69:127-34.
27. Sakaki T, Naruse H, Masai M, Takahashi K, Ohyanagi M, Iwasaki T, *et al*. Cilnidipine as an agent to lower blood pressure without sympathetic nervous activation as demonstrated by iodine-123 metaiodobenzylguanidine imaging in rat hearts. Ann Nucl Med 2003;17:321-6.
28. Sakata K, Shirotani M, Yoshida H, Nawada R, Obayashi K, Togi K, *et al.* Effects of amlodipine and cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. Hypertension 1999;33:1447-52.
29. Xu GL, Hui X, Wu HD, Ling Q. A meta-analysis of the efficacy and safety of cilnidipine in Chinese patients with mild to moderate essential hypertension. Afr J Pharm Pharmacol 2012;6:2393-9.

How to cite this article: Adake P, Somashekar HS, Mohammed Rafeeq PK, Umar D, Basheer B, Baroudi K. Comparison of amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in mild to moderate hypertensive individuals: A prospective study. J Adv Pharm Technol Res 2015;6:81-5.

Source of Support: Nil, **Conflict of Interest:** Nil.