ORIGINAL RESEARCH

Assessment of tolerability of Cilnidipine and Amlodipine in the treatment of hypertension

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Abstract
Background: To assess the tolerability of Cilnidipine and Amlodipine in the treatment of hypertension.**Materials & Methods:**A total of 40 patients with newly diagnosed mild to moderate hypertension. Comprehensive demographic information was collected for all participants. A complete evaluation of the cardiovascular and respiratory systems was also performed. Follow-up examinations took place at the 2nd, 4th, and 6th weeks. All data were recorded in a Microsoft Excel sheet and subjected to statistical analysis using SPSS software. The significance level was assessed using the Student t-test and chi-square test.**Results:**Forty patients were included in the study, divided evenly into two groups, with 20 patients in each group. The mean age of patients in Group C and Group A was 46.2 years and 40.2 years, respectively. Comparing the tolerability of the drugs between the two study groups yielded non-significant results.**Conclusion:**Patients experiencing hypertension demonstrated greater tolerability with Cilnidipine when contrasted with Amlodipine.
Keywords: Amlodipine, Hypertension, Cilnidipine.

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] In India, 29.8% population are suffering from hypertension. [3]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. [4] Hypertension represents a potent risk factor for cardiovascular, peripheral vascular, and renal diseases. [5,6]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 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.[7,8]

Hypertension is a key modifiable risk factor for cardiovascular mortality and morbidity and it is considered to be silent diseases, whose symptoms are not noticeable until and unless the disease is in an advanced phase. Globally, one billion people are suffering from hypertension. [9] In India, about 33% urban and 25% rural populations are hypertensive. [10] The increase in the prevalence of hypertension is dependent on numerous interlinked factors such as urbanization with associated changes in lifestyle and food habits, ageing and social stress. [10]

Amlodipine is third generation CCB with an excellent pharmacological profile. The major drawback of amlodipine is, it induces pedal oedema. [11] Chronic therapy of amlodipine enhances the release of more catecholamines from sympathetic nerve terminals, [12] few clinical studies showed that amlodipine enhances the release of more endothelial nitric oxides, [13] and decreases the Atrial Natriuretic Peptide (ANP). [14] Cilnidipine is a fourth generation L/N type of CCB, which blocks the N-type of calcium channels at the

sympathetic nerve endings and decreases the release of catecholamines and by blocking L-type calcium channels relaxes arteriolar smooth muscles, which decreases the peripheral vascular resistance. [15] In the kidney, cilnidipine reduces the proteinuria by relaxing both afferent and efferent arterioles. [16] Hence, this study was conducted to assess the tolerability of Cilnidipine and Amlodipine in the treatment of hypertension.

MATERIALS & METHODS

A total of 40 patients with newly diagnosed mild to moderate hypertension. Comprehensive demographic information was collected for all participants. Through random allocation, the patients were divided into two groups, each consisting of 20 individuals:

Group A: Received Tab Amlodipine with a dosage of 2.5mg

Group C: Received Tab Cilnidipine with a dosage of 5mg

A thorough general physical examination and systemic assessment were conducted. Blood pressure on the radial pulse was measured in an upright position using a Mercury Sphygmomanometer. A complete evaluation of the cardiovascular and respiratory systems was also performed. Follow-up examinations took place at the 2nd, 4th, and 6th weeks. All data were recorded in a Microsoft Excel sheet and subjected to statistical analysis using SPSS software. The significance level was assessed using the Student t-test and chi-square test.

RESULTS

Forty patients were included in the study, divided evenly into two groups, with 20 patients in each group. The mean age of patients in Group C and Group A was 46.2 years and 40.2 years, respectively. The majority of subjects in both study groups were male. Pedal edema was observed in 15 percent of subjects in Group A. Headache and gastrointestinal disturbances were reported in 5 percent of subjects each in Group C, and in 10 percent and 20 percent of subjects, respectively, in Group A. Hypotension and palpitations were noted in 20 percent and 5 percent of patients, respectively, in Group C, and in 15 percent and 10 percent of subjects, respectively, in Group A. Comparing the tolerability of the drugs between the two study groups yielded non-significant results. However, a slightly higher incidence of adverse reactions was observed among patients in the amlodipine group.

Table 1: Demographic data

Data		Group C		Group A		p-value
		Number	Percentage	Number	Percentage	
Age group (years)	Less than 40	8	35	7	35	0.3
	More than 40	13	65	13	65	
Gender	Male	11	55	14	70	0.8
	Female	9	45	6	30	

Table 2: Adverse events

Adverse events	Group C		Group A		p-value
	Number	Percentage	Number	Percentage	
Pedal edema	0	0	3	15	-
Headache	1	5	2	10	0.2
GI Disturbance	1	5	4	20	0.4
Dizziness	0	0	1	5	0.4
Hypotension	4	20	3	15	1
Palpitation	1	5	2	10	0.2
Myalgia	1	5	0	0	0.5
Blurring vision	1	5	2	10	1
Nausea/vomiting	3	15	1	5	0.4

DISCUSSION

Cilnidipine is an L/N-type calcium channel blocker, which lowers the BP in part by sympathetic nerve inhibition at the peripheral sympathetic nerve endings in vivo.[17] It has been shown to reduce both systolic blood pressure (SBP) and diastolic blood pressure (DBP) but does not increase pulse rates (PR) or plasma catecholamines.[18] It has also been shown to inhibit the pressor response to the acute cold stress in spontaneously hypertensive rats (SHR). [19] Cilnidipine was reported to be effective in hypertensive patients with morning HTN in which sympathetic nerve overactivity was potentially involved. In hypertensive patients with abnormal nocturnal BP, Cilnidipine was also shown to significantly lower the BP, especially during sleep when exaggerated activation of the sympathetic nerve occurs. [20] Cilnidipine also attenuates vascular endothelial dysfunction and thus is useful in the long-term management of cardiovascular disorders.[21] The anti-hypertensive effects of Cilnidipine are significant, with good oral absorption and a long duration of action. After oral

administration, drug concentrations peak at 1.8 to 2.2 hours and show a half-life of 7.5 hours. However, despite a shorter half-life, Cilnidipine exhibits a prolonged duration of anti-hypertensive action. It is postulated that Cilnidipine exhibits a high protein binding of 98%, which prolongs the duration of action. In-vitro and animal studies have shown that Cilnidipine action is slower in development and longer in duration compared to Nifedipine and Nicardipine. Hence, this study was conducted to assess the tolerability of Cilnidipine and Amlodipine in the treatment of hypertension.[22]

In the present study,forty patients were included in the study, divided evenly into two groups, with 20 patients in each group. The mean age of patients in Group C and Group A was 46.2 years and 40.2 years, respectively. The majority of subjects in both study groups were male.A study by Shetty R et al, to determine whether cilnidipine can produce resolution of amlodipine-induced edema while maintaining adequate control of hypertension. There was no significant change in mean arterial blood pressure and pulse rate. Therapy with cilnidipine resulted in complete resolution of amlodipine-induced edema in all the cases without significant worsening of hypertension or tachycardia. Cilnidipine is an acceptable alternative antihypertensive for patients with amlodipine-induced edema. [23]

In the present study,pedal edema was observed in 15 percent of subjects in Group A. Headache and gastrointestinal disturbances were reported in 5 percent of subjects each in Group C, and in 10 percent and 20 percent of subjects, respectively, in Group A. Hypotension and palpitations were noted in 20 percent and 5 percent of patients, respectively, in Group C, and in 15 percent and 10 percent of subjects, respectively, in Group A. Comparing the tolerability of the drugs between the two study groups yielded non-significant results. However, a slightly higher incidence of adverse reactions was observed among patients in the amlodipine group. Another study by Shetty K et al, studied the clinical and biochemical profile in Amlodipine and Cilnidipine treated mild to moderate hypertensive patients. A total of 140 mild to moderate hypertensive patients (HTN classified according to Joint National Committee-8 (JNC-8) HTN guideline), 70 were in Amlodipine group (Group-A), and other 70 patients were in Cilnidipine group (Group-B). Group-A receiving Tab Amlodac 5 mg/day and Group-B receiving Tab Cilacar 10 mg/day, and both the group receiving respective medications since more than six months. Cilnidipine group showed comparatively shortened QT/QTc interval than the Amlodipine group. [24] Amlodipine is a long-acting, lipophilic, third generation dihydropyridine (DHP) CCBs that exerts its action through inhibition of calcium influx into vascular smooth muscle cells and myocardial cells, which results in decreased peripheral vascular resistance (PVR). Amlodipine is indicated for the treatment of high blood pressure (BP)/HTN and angina. In addition, a number of randomised trials have ascertained its utility in angina pectoris. [25] Amlodipine is usually dosed on a once daily basis because of its long half-life, which is favourable for patient compliance. A starting dose of 5 mg is usually recommended with a maximum daily dose of 10 mg. In the elderly population and those with hepatic failure, a starting dose of 2.5 mg is recommended. Amlodipine has a gradual onset of action and hence no significant reflex neuroendocrine activation. If amlodipine is discontinued, BP generally returns to baseline over 1 week without any dangerous rebound elevations in BP (unlike clonidine). [26] Adake P et al, compared amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in hypertensive individuals. 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. [27] 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. [28] It is used as an antihypertensive agent with a long duration of action that allows once-daily dosing. [29] Cilnidipine is known to suppress catecholamine release from peripheral sympathetic nerves as it blocks N-type channels in sympathetic nerve terminals as well as having a common L-type calcium channel-blocking effect. [30] It has been shown that cilnidipine does not cause coronary sympathetic hypertonia in response to blood pressure reduction, unlike L-type channel blockers. [31] When administered to the patients with essential hypertension, cilnidipine suppressed cardiac sympathetic over activity and an increase of heart rate with blood pressure reduction. [32] 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.[33]

CONCLUSION

Patients experiencing hypertension demonstrated greater tolerability with Cilnidipine when contrasted with Amlodipine.

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