Research Article

A clinical study of the effects of cilnidipine and amlodipine in hypertensive patient focusing on pedal edema

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Abstract

Introduction: Many Calcium channel blocker drugs for control of hypertension are available. New drug Cilinidipine is available and approved for treatment of hypertension. It acts by blocking both L-type and N-type voltage-dependent calcium channels. The neural N-type blockade leads to stoppage of the secretion of norepinephrine and it also depresses sympathetic nervous system activity. The aim of the study is to assess the effect of cilnidipine and amlodipine on hypertensive patient. **Method:** Clinidipine (n=50) and Amolodipine (n=50) were given once daily and BP was measured daily before and after the medicine in 100 hypertensive patients on OPD basis in GDMC, Dehradun. **Result:** Only 4 patients (n=50; 8%) in cilnidipine group developed edema within 10 days of therapy, while 32 patients (n=50, 64%) developed with edema within 10 days of treatment in amlodipine group. **Conclusion:** Cilnidipine is also associated with less incidences of pedal edema which is main complaint of patient. It controls BP better with less reflex tachycardia and decrease in morning surge.

Key words: Cilnidipine, BP, Calcium antagonists.

Introduction

BP control reduces the target organ damage and improves the clinical outcome in patients with hypertension [1−6]. In Japan calcium antagonists (Amlodipine) have been widely used for the treatment of hypertension [7, 8]. Short-acting calcium channel blocker causes sympathetic activity and reflex tachycardia while Amlodipine because of its long duration of action avoids [9]. Amlodipine controls BP levels throughout a 24-h period [10, 11].

Cilnidipine is a new drug of Calcium Channel blocker group and blocks both L-typeand N-type voltage-dependent calcium channels [12]. The N-type voltage-dependent calcium channel regulates the release of norepinephrine from sympathetic nerve endings [13]. Once-daily administration of cilnidipine results in BP decrease without reflex tachycardia than similar administration than once-daily administration of nifedipine [14,15]. The morning rise in BP increases the risk of stroke independent of age and 24-h BP level in hypertensive patients significantly [16]. Amlodipine due to its long duration of action, controls 24-BP and it is associated with morning rise which is useful for the prevention of cardiovascular events in hypertensive patients. Sympathetic nervous activity is high in the morning, and may contribute to morning BP surge [17], and cilnidipine, due to N-type calcium channel blockade, causes morning rise BP.

Cilnidipine and Amlodipine have clinical benefits resulting from the unique characteristics of each agent. We compared the effects of cilnidipine and amlodipine on ambulatory BP and pulse rate (PR) monitoring in patients (n=100) with essential hypertension.

Methods

We correlated by an open-label, randomized study of the effects of once-daily morning administration of cilnidipine and amlodipine on ambulatory BP. 100 hypertensive outpatients with systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg on two or

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more occasions were included in the study. The studied patients were randomly selected from outpatients who met the following criteria. No antihypertensive patients received medication for last one month before the start of the study.

The physical examination was done and blood and urine tests, chest X-ray, and a resting electrocardiogram, were done and were normal. Renal and liver function was normal. There was no patient having history of coronary artery disease, stroke (including transient ischemic attack), congestive heart failure, or malignancy. All patients were well informed and consent was taken from all of the subjects.

Approval from Ethical Committee was taken. One hundred and ten patients were studies for this study.

10mg once a day clilnidipine was given orally for one month. Amlodipine 5 mg was given orally once daily for 4 weeks. We do not increase the dosage of amlodipine and clinidipine. Each patient was studied for 16 weeks.

The BP was monitored by LCD BP instrument 8.00 AM and 8.00 PM before starting of treatment and then at 16 week. Morning BP was defined as the mean BP during the first 2 h after awakening.

Results

Total 100 patients included and completed the study. Patient's age for amlodipine group ranged between 30 to 60 years and 32 to 64 cilnidipine group [Table 1]. Women (n = 28) were more than men (n = 22) in both the study groups. Both the groups were compared.

Table-1: Distribution of patients.

Patients	Amlodipine	Cilinidipine	Total
Number	50	50	100
Age (Years) range	30-60	32-64	31-62
Gender			
Male	22	22	44
Female	28	28	56

SBP and DBP ($P < 0.05$) reduction was appropriate in both groups compared to baseline data [Table 2]. Efficacy in both group was similar($P > 0.05$).

Table-2: Variation in blood pressure after treatment.

BP	Treatment	Pre-treatment BP	Post-treatment BP	difference	p - value
SBP	Amlodipine	166±8	140±10	26±9.0	<0.001
	Cilnidipine	168±8	142±6	26±7.0	<0.001
DBP	Amlodipine	94±10	80±6	14±4.0	<0.001
	Cilnidipine	98±7	84±6	14±1.0	<0.001

Only 4 patients (n=50; 8%) in cilnidipine group developed edema within 10 of therapy, while 32 patients (n=50, 64%) developed with edema within 10 days of treatment in amlodipine group (Table 3).

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).

Table-3: Edema in both group.

Drug	Edema (%)	Without edema (%)	Total	p-value
Amlodipine	32 (64%)	18 (36%)	50	<0.001
Cilnidipine	4 (8%)	46 (92%)	50	<0.001
Total	**36 (36%)**	**64 (64%)**	**100**	

Statistical analysis- Antihypertensive efficacy between two groups was compared by unpaired *t*-test.

Discussion

Cilnidipine or amlodipine are used in treatment of hypertension and reduce the ambulatory BP and morning BP. Cilnidipine, does not increase in pulse rate [18, 19]. Cilnidipine causes significantly decrease in Pulse Rate than amlodipine treatment in hypertensive patients. It is well documented that a higher heart rate is associated with a long-term risk of cardiovascular mortality, independent of other cardiac risk factors [20]. Therefore, antihypertensive drugs not causing tachycardia are preferred drug of treatment of hypertension. It has been reported that treatment with short-acting calcium antagonists may not prevent cardiovascular disease [21, 22].

Gradual BP reduction is desirable and rapid fall in BP and an increase in sympathetic activity have been suggested as possible underlying mechanisms for this unexpected outcome [23]. Long acting calcium channel blockers that exert less influence on the sympathetic activity are now recommended for treatment of hypertension [24].

The long-acting nature of amlodipine (which has a half-life of 45 h after a single oral dose [25], leads to a reduction of BP throughout the day and night [10], and prevents an increase in sympathetic activity [26]. In our study, increase in PR by amlodipine was significant.

Recently, some studies have reported that amlodipine increased PR, sympathetic activity, and reflex tachycardia via a reduction in BP, which are common adverse effects of conventional dihydropyridine calcium antagonists [27, 28]. Changes of PR is dose dependent.

Lowering of BP was associated with a significant fall in cardiovascular events [29]. Therefore, in hypertensive treatment, it is not clear whether the reduction of PR is more effective in the prevention of cardiovascular events than the reduction of BP.

Cilnidipine is also a long-acting dihydropyridine calcium antagonist and it is associated with reduction of pulse rate along with significant reduction of BP. Both amlodipine and cilnidipine have been applied clinically based on their ability to blockade both the L-type and N-type calcium channels [18]. Cilnidipine is significantly more selective in blocking the N-type calcium channel than other calcium antagonists [14, 15, 18, 19, 26, 31, and 32]. Blockade of the neural N-type calcium channel inhibits the secretion of norepinephrine from peripheral neural terminals [12]. As sympathetic

activity is not increased by blocking the N-type calcium channels with cilnidipine, it may be the cause a decrease in PR. Clinically, Sakata et al. demonstrated by using 123I-metaiodobenzylguanidine cardiac imaging that cilnidipine suppressed cardiac sympathetic overactivity while amlodipine had little suppressive effect [18].

In this study, we could not prove this hypothesis because we did not measure an index of sympathetic nervous activity in our study. Morning BP surge were associated with target organ damage [33] and stroke events in hypertensive patients [16]. The treatment of morning BP is very important. Whereas arousal from sleep is associated with a slight rise in plasma epinephrine, arising induces a significant rise in both epinephrine and norepinephrine. We speculated that cilnidipine therapy with its sympathetic inhibitory action was more effective than amlodipine therapy in controlling morning BP in hypertensive patients.

Generally speaking, there have been problems with the reproducibility of ABPM. Nonetheless, some reports have shown that ABPM was useful for evaluating the BP-lowering effects of antihypertensive drugs. In conclusion, N-type calcium channel blockade by

cilnidipine may not cause reflex tachycardia, and may be useful for hypertensive treatment.

Conclusion

Cilnidipine is also associated with less incidences of pedal edema which is main complaint of patient. It controls BP better with less reflex tachycardia and decrease in morning surge. Thus, Cilnidipine is better antihypertensive drug than amlodipine.

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