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Research Article

Replacement of Amlodipine with Cilnidipine and assessment of pedal edema along with blood pressure control

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Abstract: Amlodipine, an L- type calcium channel blocker (CCB) is the most commonly used antihypertensive drug. Pedal edema is a common adverse effect of amlodipine. Cilnidipine, a newer L/N-type CCB, is also an effective antihypertensive. The Aim of this study was to determine whether cilnidipine can resolve amlodipine-induced edema along with adequate control of hypertension. This was a prospective, observational study done at the tertiary care centre of Central India. A total number of 50 (n = 50) patients of essential hypertension with amlodipine-induced edema of either gender, attending outpatient department of medicine, were included in the study. Concomitant nephropathy, cardiac failure, hepatic cirrhosis, or other causes of edema, and secondary hypertension were excluded by appropriate tests. Amlodipine therapy was substituted in all the cases with an efficacy-equivalent dose of cilnidipine. Clinical assessment of pedal edema and measurement of bilateral ankle circumference, body weight, blood pressure, and pulse rate were performed at onset of the study and after 4 weeks of cilnidipine therapy. At completion of the study, edema had resolved in all the patients. There was a significant decrease in bilateral ankle circumference and body weight ($P < 0.001$). 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 worsening of hypertension or tachycardia. Cilnidipine is an acceptable alternative antihypertensive for patients with amlodipine-induced edema.
Keywords: Ankle edema, Amlodipine, Cilnidipine

INTRODUCTION

Hypertension is the most common cardiovascular disease. In India, 29.8% population are suffering from hypertension [1]. Hypertension represents a potent risk factor for cardiovascular, peripheral vascular, and renal diseases [2-6]. Pedal edema is a common adverse effect of amlodipine, a widely used L-type calcium channel blocker (CCB), seen in up to 15% of patients receiving the drug [7].

The usual approach to patients with amlodipine-induced edema involves cessation of amlodipine therapy and substitution with an alternative antihypertensive. Cilnidipine is a third generation L/N-type CCB [8] and is approved for the therapy of essential hypertension. A recent meta-analysis on the efficacy and safety of cilnidipine has demonstrated good tolerability and an antihypertensive efficacy equivalent to amlodipine [9]. This study was, therefore, planned to determine whether cilnidipine therapy can produce resolution of amlodipine-induced edema while maintaining adequate control of blood pressure.

SUBJECTS AND METHODS

This prospective, observational study conducted at the tertiary care centre of Central India between April 2015 and June 2015.

Inclusion criteria

All patients of hypertension who were taking amlodipine and have developed amlodipine induced pedal edema.

Exclusion criteria

Patients with preexisting edema, cor pulmonale, nephrotic syndrome, hypoproteinemia, anemia, pregnant women, varicose veins and who are on drugs such as nonsteroidal anti-inflammatory drugs were excluded from study.

Study Procedure

A total 50 patients (n = 50) 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. Baseline parameters including clinical evidence of ankle edema, pulse rate, blood pressure, bilateral ankle circumference, and body weight were recorded for all patients. Ankle circumference was determined with a tape measure, 1 cm above the medial malleolus, with the patient standing. The included patients typically maintained control of hypertension with either amlodipine alone or combinations with other anthypertensives.

All patients were then initiated on an efficacy-equivalent dose of cilnidipine (5 mg of amlodipine is equivalent to 10 mg of cilnidipine). Amlodipine therapy was stopped on the day of initiating cilnidipine. The patients were followed-up for four weeks. Relevant parameters were then recorded again for all the patients.

Statistical Analysis

Data analysis was done with Statistical Product and Service Solutions (SPSS) Statistics version 17.0 (Chicago IL, USA). Continuous variables were presented as median with interquartile range (IQR) or mean ± standard deviation. Wilcoxon signed-rank test was used to compare the means of variables before and after administration of cilnidipine. P <0.05 were considered indicative of statistical significance.

RESULTS

Of the 50 patients included in the study, 22 (44 %) were male. The mean age was 55 years(± 2.6 SD). Mean duration of therapy with amlodipine at the time of inclusion in the study was 12 months. Forty five patients (90 %) were receiving 5 mg of amlodipine daily. Baseline hemodynamic data, ankle circumferences, and body weight are detailed in Table-1.

Table-1:

Sr. No.	Parameters	Measurement at baseline (On Amlodipine) Mean ± SD	Measurement after 4 weeks (On Cilnidipine) Mean ± SD	Change in value	P value
1.	Ankle circumference, right (cm)	27.0 ± 1.08	23.07 ± 0.99	3.93	< 0.001
2.	Ankle circumference, left (cm)	26.98 ± 1.01	23.08 ± 0.97	3.90	< 0.001
3.	Body weight (kg)	76.7 ± 2.6	72.6 ± 1.8	4.1	
4.	Pulse rate (bpm)	89 ± 5	87 ± 4	2	
5.	Mean systolic blood pressure (mm Hg)	124 ± 3.8	123.3 ± 2.9	0.7	
6.	Mean diastolic blood pressure (mm Hg)	78.9 ± 2.6	76.8 ± 1.9	2.1	

Reassessment after 1 month showed complete clinical resolution of ankle edema in all 50 patients. There was a significant decrease in ankle circumference and body weight. Comparison of hemodynamic parameters revealed a non-significant rise in mean arterial blood pressure, and no significant change in pulse rate.

DISCUSSION

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 [10]. Pedal edema causes anxiety among patients and increases drug discontinuation rate.

A number of mechanisms have been postulated for CCB-induced edema. The principal mechanism involves interference of normal auto-regulatory postural vasoconstrictor reflexes [11]. In healthy individuals, reflex pre-capillary vasoconstriction in response to venous congestion protects the capillary bed from increased blood pressure, thereby restricting hydrostatic filtration of fluid into the interstitium. L-type CCBs like amlodipine directly inhibit pre-capillary vasoconstriction through arteriolar dilatation, thus promoting interstitial edema. Other contributory mechanisms include capillary hypertension and increased microvascular permeability. In contrast to amlodipine which acts primarily through blockade of L-type Ca^{2+} channels, cilnidipine acts through dual blockade of L-type and N-type Ca^{2+} channels [12]. Whereas L-type Ca^{2+} channel blockade produces vasodilation of peripheral resistance vessels akin to amlodipine, inhibition of neuronal N-type Ca^{2+} channels

disrupts sympathetic nervous outflow, lowering plasma catecholamine levels, and thereby producing further vasodilatation. This unique mechanism of action results in vasodilation of both pre- and post-capillary resistance vessels reducing capillary hypertension and consequent hyperfiltration of fluid into the interstitium. The superior renoprotection of cilnidipine over other CCBs [13] through attenuation of glomerular hyperfiltration has been attributed to sympathetic blockade [14] and inhibition of N-type Ca^{2+} channels [15]. Reduction of capillary hyperfiltration in the peripheral systemic circulation would appear to be an extension of the same phenomenon. The dual mechanisms of cilnidipine can therefore explain both the low incidence of ankle edema and the excellent antihypertensive action that it possesses. Reduced inhibition of the local vasoconstrictor reflexes that normally prevent excessive fluid filtration in dependent regions could also contribute to the lack of edema with cilnidipine therapy; further studies are required to elucidate this possibility. Shetty R et al. showed complete clinical resolution of ankle edema in all 27 hypertensive patients after switching them from amlodipine to cilnidipine [16].

CONCLUSION

Cilnidipine is an effective and well-tolerated alternative antihypertensive in patients with amlodipine-induced edema.

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