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Calcium channel blockers induced pedal edema; mechanism and treatment options: Review

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Abstract

Hypertension is one of the most common clinical conditions encountered by the physicians. There are wide ranges of medications available for treatment of hypertension, in which Calcium Channel Blockers (CCBs) are the one of the most commonly prescribing drug. The first generation antihypertensive drug nifedipine was introduced in 1960s; due to its rapid vasodilatory action it enhances the sympathetic tone. The second and the third generation drugs showed the reduction of sympathetic reflex by its slow-releasing action.

Amlodipine which was introduced as the third generation, exhibits longer half-life and most potent antihypertensive agent as compared to the previous generation agents. Ankle edema is one of the most frequent adverse effects of amlodipine often leading to noncompliance and discontinuation of an effective antihypertensive drug. Cilnidipine is a fourth generation calcium channel blocker with unique features, which inhibits both sympathetic N-type and vascular L-type Ca2+ channels. Interestingly, Cilnidipine shows complete resolution of amlodipine induced pedal edema in clinical practice. Therefore, this strategy may provide a new approach for the treatment of cardiovascular diseases. This review article is aiming to explain the calcium channel blocker - associated edema and resolution of edema through the use of L and N-type of calcium channel blockers. CCBs are potential antihypertensive agents but the main drawback of this group of drug is it produces pedal edema which decreases the compliance. The main cause for CCB-induced edema increased capillary hydrostatic pressure by arteriolar dilation. The new L and N-type of CCB cause pre and post capillary dilatation which normalizes the hydrostatic pressure, which resolves the edema.

Keywords: Pedal edema, Amlodipine, Cilnidipine, Calcium Channel Blockers

Introduction

Hypertension is one of the major global health care challenges because of its devastating health consequences and difficulties involved in its treatment. It is the leading cause for premature death worldwide. The global burden of Hypertension is extremely high, about 80% of this burden being in developing countries. More than 1 billion adults worldwide are

diagnosed to have hypertension, which is projected to increase 1.5 billion by the year 2025. It accounts for more than 9 million deaths annually(1)(2). In most instances hypertension being asymptomatic, early detection and treatment of this condition will reduce the adverse health events and improves the quality of life.

High blood pressure is be controlled by changing lifestyle modification or with medications. Lifestylemodifications include weight reduction, quitting smoking, maintain a healthy diet and regular exercise, reducing sodium intake, restriction of alcohol consumption. Interventional modalities include several classes of drugs. Calcium channel blockers (CCBs), Angiotensin converting enzyme (ACE) inhibitors, Angiotensin receptor blockers(ARBs), β-Blockers, Diuretics, α-Blockers and peripheral vasodilators are used as a monotherapy and also in combination therapy(3).

Calcium channel blockers (CCBs), which targets the voltage-dependent calcium channels (VDC) are one of the most widely used antihypertensive agents. Calcium channels are widely distributed throughout the body and play a critical role in maintenance of vascular tone. CCBs are classified into several sub types depending on their electrophysiological and pharmacological properties. The subtype includes L-type, N-type, T-type, P/Q-type and R-type(4). CCBs of Dihydropyridine (DHP) groups are most widely used either alone or as a principal agent in the combination therapy for treatment of hypertension.

Amlodipine, a Dihydropyridine group of calcium channel blockers (CCB) is a powerful, long acting, well-tolerated and safe antihypertensive agent. It is one of the widely used antihypertensive agents. Ankle edema is one of the most frequent adverse effects of amlodipine. It is uncomfortable, sometime intolerable and may cause considerable discomfort and disfigurement. This serious consequence leads to noncompliance and discontinuation of very effective antihypertensive drug in significant number of patients. Co-administration of antihypertensive belonging to same class may help to reducing the edema but usually doesn't completely resolve it. Adding of second medication may also intensify the risk of non-adherence by increasing the pill count and possibly Edema can sometimes lead to Anasarca(5).The approach to manage the patients with amlodipine induced pedal edema includes,discontinueof the amlodipine therapy and switch to another antihypertensive agent(6). Co-administration of antihypertensive belonging to same class may help to reducing the edema but usually doesn't completely resolve it.Inducing the second set of unfavourable events. Diuretics, either loop or thiazide, are usually not effective in resolution of CCB induced pedal edema(7)(8)(9).

The mechanism of amlodipine induced pedal edema

Edema is a condition where fluid accumulates in the interstitial space. The predictable mechanism involved in edema are increased capillary hydrostatic pressure (HP), decreased plasma oncotic pressure (POP)and increased capillary permeability and obstruction of the lymphatic system. Imbalance in the hydrostatic and colloid osmotic forces across the capillary wall results in net trans-capillary filtration exceedsthe lymphatic flow. Edema occurs due to shift of fluids from intravascular compartment to extravascular. This shift is governed by starling forces. The outward force is determined by hydrostatic pressure by capillaries which is determined by arteriolar and venular vascular tone(9).

It is believed that CCB-induced edema is caused by local changes in hydrostatic forces (3). It is mainly by caused by increased capillary hydrostatic pressure. CCB have greater vasodilatory properties on arterioles than venues (figure 1). The

variation in resistance, increases hydrostatic pressures in the precapillaries and it allows fluid shifts into the interstitial compartment leading to edema(10). The long acting CCBs shows lower incidence of edema than rapid acting CCBs. Many studies have been explained that the incidence of CCBs induced pedal edema occurs at different rates. It is evident that the dose dependent ankle edema remains a typical side effects in patients receiving both established and newer CCBs.

Incidence of pedal edema with different CCBs

Number of studies have reported the incidence of pedal edema varies with different CCBs, Multicentric, double blind, parallel group study by Leonetti, showed amlodipine had a significantly higher rate of pedal edema (19%) compared with Lercanidipine and Lacidipine (11).Pedrinelli et al compared the efficacy And incidence of pedal edema with amlodipine and lercanidipine in patients with mild to moderate hypertension. Both study drug groups achieves a significant decrease in blood pressure but amlodipine treated study group had higher incidence of pedal edema (two time greater than that of lercanidipine treated group) (12).Lund-Johansen et al. also reported higher incidence of pedal edema in hypertensive post- menopausal women when compared to Lercanidipine.

Treatment for calcium channel blocker induced pedal edema

As calcium channel blocker induced pedal edema is mainly related to vasodilation and not by fluid over load (13).Co-administration of diuretic agents is not a logical treatment to reduce peripheral edema. The drugs that decreases the intracapillary pressure by dilating the post capillary vessels are ideally suited for the prevention or reversal of pedal edema (3).

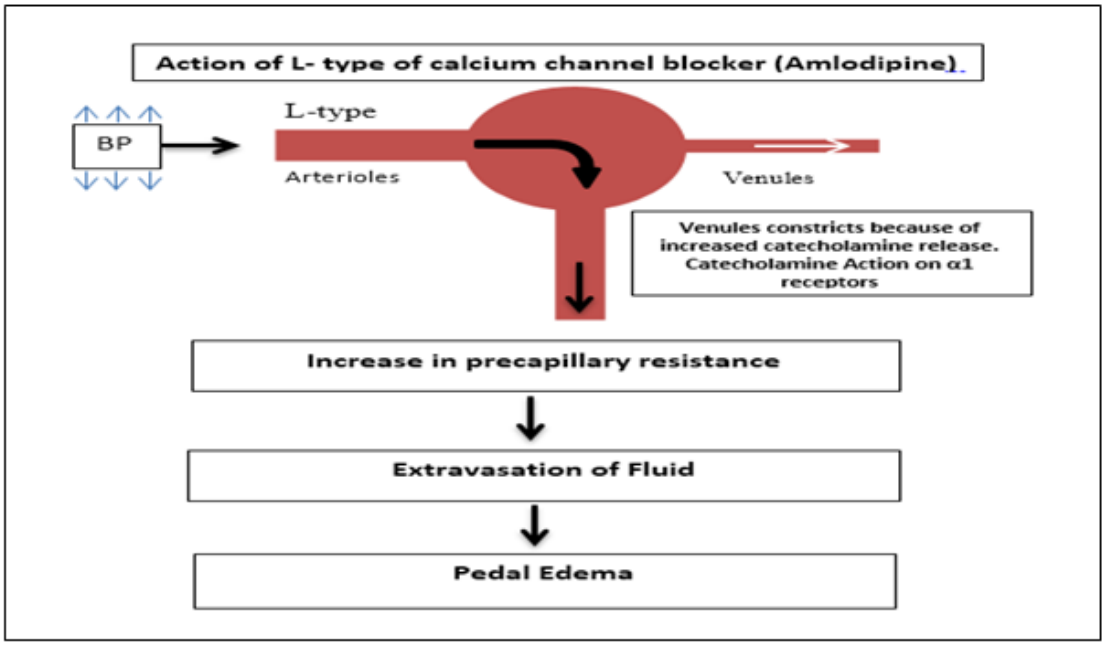

Fig. 1: Schematic diagram showing mechanism of amlodipine induced edema. Amlodipine causes vasodilatation of the arterioles and not venules causing increased capillary hydrostatic pressures leading to edema.

CCBs in combination with ACEI/ARB

Considerably lower incidence of amlodipine induced pedal edema noticed in clinical trials of CCBs with combination of ARBs and ACEIs than with CCBmonotherapy (3). A meta-analysis that compared of amlodipine monotherapy with combination therapy regimens concluded that amlodipine monotherapy was associated with a higher incidence of peripheral edema. Table 1 is a compilation of the 8 studies comparing amlodipine monotherapy with amlodipine in combination with ACEI/ARB, clearly suggesting a lower incidence of pedal edema in monotherapygroup [table 1].

Cilnidipine is suitable alternative for patients with amlodipine induced pedal edema

Cilnidipine is a fourth generation CCBs with unique pharmacological profile; i.e. dual L/N-type calcium channel-blocking action. The blockade of N-type calcium channels effectively suppresses neurohumoral regulation in the cardiovascular system, including sympathetic nervous system and rennin angiotensin system (RAAS) system. Thissympatholytic profile of Cilnidipine causes vasodilation (preventing sympathetic mediated vasoconstriction) along with arteriolar dilatation resulting in decrease capillary hydrostatic pressure thus edema (figure 2). This action similar to than seen in ARB/ACEI combination, hence it is likely to have lesser incidence of pedal edema (14).The basic approach to manage the patients with amlodipine induced pedal edema involves stop of amlodipine therapy and switch of another anti-hypertensive agents. Substitution of amlodipine with Cilnidipine can be a better strategy as it provides similar control of blood pressure. Shetty et al. conducted a study on 27 patients with essential hypertension with amlodipine induced pedal edema, in whom amlodipine was substituted with efficacy equivalent dose of Cilnidipine.

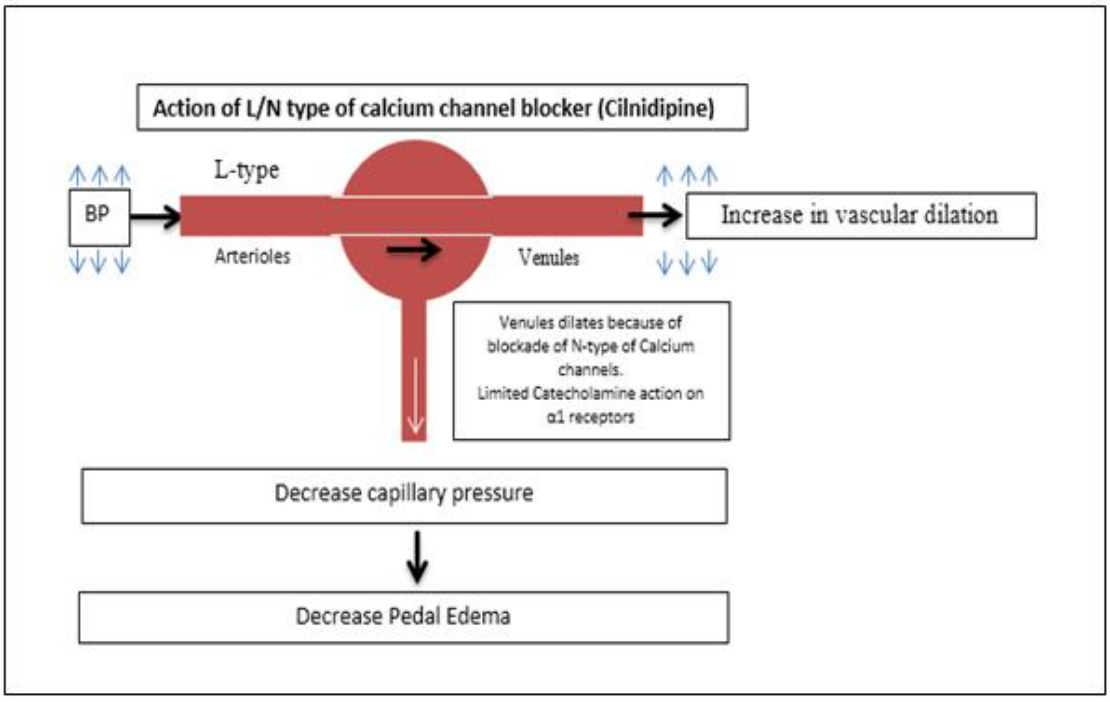

Fig. 2: Schematic diagram showing mechanism of cilnidipine. It causes vasodilatation of the arterioles venules by decreasing sympathetic mediated vasoconstriction by N type calcium channels. This results in decreased capillary hydrostatic pressures leading resolution of pedal edema.

Table 1: Shows the rates of oedema from eight relevant clinical trials. Although the incidence of oedema recorded in the CCB monotherapy groups varies widely (range, 4.9–34.4%), the data are consistent in showing lower rates of this side effect in the patients who receive ACEI/CCB or ARB/CCB combination therapy.

Reference	Trial design	CCB monotherapy			CCB combination therapy		
		Regimen and treatment duration	N	Incidence of oedema (%)	Regimen and treatment duration	N	Incidence of oedema (%)
Kuschnir et al.	Placebo-controlled, double-blind, randomized, parallel group	Amlodipine 5mg od; 8 weeks	77	16.9	Amlodipine 5 mg + benazepril 20mg od; 8 weeks	77	7.8
Messerli et al.	Single/double-blind, randomized, forced titration	Amlodipine 5mg od; 4 weeks	144	4.9	Amlodipine 5 mg + benazepril 20mg od; 8 weeks	137	1.5
Messerli et al.	Single/double-blind, randomized, forced titration	Amlodipine 5mg od; 4 weeks	144	4.9	Amlodipine 5 mg+ benazepril 10mg od; 8 weeks	138	2.2
Fogari et al.	Double-blind, randomized, crossover	Amlodipine 5mg od; 4 weeks	32	34.4	Amlodipine 5 mg+ benazepril 10mg od; 4 weeks	32	9.4
Chrysant et al.	Placebo-controlled, double-blind, randomized, factorial	Amlodipine 10mg od; 8 weeks	163	24.5	Amlodipine 10 mg+olmesartan medoxomil 40mg od; 8 weeks	162	11.2
Fogari et al.	Open-label, randomized, crossover	Amlodipine 10mg od; 6 weeks	80	30	Amlodipine 10 mg+valsartan 160mg od; 6 weeks	80	7.5
Fogari et al.	Randomized, crossover	Manidipine 10mg od; 6 weeks	40	7.5	Manidipine 10 mg+delapril 30mg od; 6 weeks	10	2.5
Philipp et al.	Placebo-controlled, double-blind, randomized, parallel group	Amlodipine 2.5, 5 or 10mg od; 8 weeks	460	8.7	Amlodipine 2.5, 5 or 10 mg+valsartan 40, 80, 160, or 320mg od; 8 weeks	1437	5.4

Outcome measures changes from baseline in blood pressure, pulse rate, ankle circumference, and body weight after four weeks of treatment with Cilnidipine. Study findings are all patients showed resolution of edema after switching from amlodipine to Cilnidipine. No significant difference in mean arterial blood pressure and pulse rate were reported after the substitution with Cilnidipine significant reduction was observed in bilateral ankle circumference and body weight, highlighting the possible role of cilnidipine in treatment of amlodipine induced pedal edema.

Conclusions

Antihypertensive agents are effective in the prevention and long-term serious cardiovascular disorders, stroke, and renal disease in patients with hypertension. Despite the availability of numerous effective antihypertensive medications, many patients have poorly controlled BP. Amlodipine is the long acting and well tolerated drug but the main drawback of this drug is incidence of pedal edema . It has beenshown that using an ACE inhibitor along with a DHP CCB has shown to decrease pedal edema. ARB hasan effect similar to that of the ACE inhibitors, but has been less well documented. Cilnidipine is a promising calcium channel blocker as the 4th generation with a rational pharmacological profile; effectively suppresses neurohumoral regulation in the cardiovascular system, including sympathetic nervous system and renin-angiotensin-aldosterone system. Cilnidipine has showed great deal of promise in resolution of amlodipine induced pedal edema with good efficacy.

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Conflict of interests: Nil

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