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General Medicine

NOT SO INNOCENT AS PORTRAYED: CILNIDIPINE- INDUCED PEDAL EDEMA—A CASE SERIES

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ABSTRACT **Background:** Cilnidipine, a dual calcium channel blocker, is increasingly prescribed for hypertension and related cardiovascular conditions. However, peripheral edema is a known adverse effect associated with calcium channel blockers, and its incidence with cilnidipine remains underreported. **Objective:** This case series aims to highlight the occurrence of pedal edema in patients treated with cilnidipine, contributing to the understanding of its safety profile. **Observations:** We present six cases of patients who developed pedal edema following the initiation of cilnidipine therapy. Clinical details, including demographics, medical history, dosage, duration of treatment, and management strategies, were collected and analyzed. **Results:** Among the six cases, all patients were treated for hypertension. The onset of pedal edema varied from two weeks to nine months after starting cilnidipine.All patients were otherwise stable with no signs of heart failure or renal impairment. Cilnidipine was discontinued in five patients, leading to a resolution of edema within a maximum of 2 weeks, while the remaining one continued therapy with dose adjustment, resulting in partial resolution of symptoms. **Conclusion:** Pedal edema can occur in patients treated with cilnidipine, and awareness of this potential side effect is essential for clinicians. Although numerous individual case reports exist on this topic, this is the first-ever case series to describe cilnidipine-induced pedal edema, underscoring the need for larger case-control studies to further investigate this side effect

KEYWORDS :

INTRODUCTION

Cilnidipine, a calcium channel blocker that selectively targets both L-type and N-type calcium channels, has gained popularity in the management of hypertension and related cardiovascular conditions. While its dual action is beneficial for controlling blood pressure and offering renal protective effects, cilnidipine is not without side effects. One notable adverse effect is peripheral edema, particularly pedal edema, which can significantly affect patients' quality of life and adherence to therapy.

Cilnidipine is increasingly being considered as an alternative to amlodipine, a widely prescribed calcium channel blocker known for its propensity to cause pedal edema in a significant number of patients[1]. Studies have indicated that amlodipine's side effect profile, particularly the incidence of peripheral edema, can be attributed to its mechanism of action, which predominantly affects vascular smooth muscle. [2,3] In contrast, cilnidipine's dual mechanism may mitigate this adverse effect, making it a compelling option for patients who are prone to edema [4]

Despite its clinical benefits, the incidence and underlying mechanisms of cilnidipine-induced edema are not well-documented, creating a knowledge gap that can impact treatment strategies. This case series presents six instances of pedal edema in patients treated with cilnidipine, aiming to enhance understanding of this phenomenon.

Methods

Data collected included demographic information, medical history, cilnidipine dosage, duration of treatment, concomitant medications, and management strategies employed.

We conducted a retrospective analysis of six Hypertensive Patients aged 40 years and older, patients who developed pedal edema after at least 2 weeks of starting cilnidipine therapy (as stand alone or as an add on to other anti-hypertensives).

We ensured that none of our six patients had other conditions contributing to pedal edema, such as heart failure, liver disease, or chronic venous insufficiency. All the patients in this case series had a serum creatinine level of less than 1.5 mg/dL. None of the patients had been treated with any other calcium channel blockers in one month prior to initiating cilnidipine.

Table 1 : Demographics And Characteristics Of Patients

Patient No.	Age	Sex	Blood pressure (During presentation of edema)	Duration of Cilnidipine use	Cilnidipine dose	Serum Creatinine	Other causes of edema
1	81	M	148/90	6 months	(Cilnidipine10mg + Metoprolol 25mg) Twice daily	1.2	None
2	67	F	134/84	3 months	Cilnidipine 5mg Twice daily	0.9	None
3	53	M	128/80	1 month	Cilnidipine 10mg + Telmisartan 40mg Once daily	0.78	None
4	70	M	146/94	2 weeks	Cilnidipine 10mg Twice daily	1.5	Microalbuminuria
5	46	F	132/78	2 months	Cilnidipine 10mg Once daily	0.84	None
6	59	M	140/88	9 months	Cilnidipine + Telmisartan+ Metoprolol	1.1	None

Case 1 : The Silent Thief of Swollen Legs

An 81-year-old male with a medical history of hypertension and diabetes was started on a combination therapy of metoprolol and cilnidipine six months prior to the onset of symptoms. The patient presented with progressively worsening edema in both lower limbs. Laboratory investigations revealed a serum creatinine level of 1.2 mg/dL and a urine microalbumin level of 0.27, with all other workup results appearing normal. After discontinuing cilnidipine, the pedal edema resolved within one week. To manage his hypertension effectively, the patient was switched to telmisartan and continued on metoprolol, resulting in no recurrence of edema.

Case 2: Friend Turned Foe: The Unforeseen Danger

A 67-year-old lady, a survivor of breast cancer who underwent surgery seven years ago, was diagnosed with hypertension and started on cilnidipine as monotherapy. Two months into the treatment, she

reported experiencing pedal edema. Although she discontinued cilnidipine on her own, the edema persisted. A short course of diuretic was prescribed, which successfully resolved the edema. Subsequently, the patient was re-initiated on cilnidipine (10 mg) in combination with chlorthalidone (6.25 mg). However, the edema reappeared within two weeks, and she additionally developed hyponatremia secondary to chlorthalidone use. Both drugs had to be discontinued and patient was switched over to olmesartan 20mg.

Case 3: A Better Sibling

A 53-year-old male with hypertension, previously controlled on telmisartan for 7 years, presented with elevated blood pressure (166/104 mmHg) and was started on a fixed-dose combination of cilnidipine and telmisartan. Despite normal renal and cardiac function, the patient developed bilateral pedal edema within one month of initiating therapy. The edema resolved within 5 days of discontinuing cilnidipine, after which he was switched to benidipine, with no recurrence of edema.

Case 4: A Dual Challenge With Amlodipine And Cilnidipine

A 70-year-old male with hypertension, diabetes, and a history of cerebrovascular accident (CVA) 5 years ago, presented with gross bilateral pedal edema. He had been on amlodipine 5 mg twice daily for blood pressure control. His renal function was mildly impaired due to poorly controlled diabetes (creatinine 1.5 mg/dL, eGFR 50 mL/min/1.73m²), with stable levels over the last 2 years. Urinalysis showed microalbuminuria (48 mg/dL), while cardiac evaluation, including an ejection fraction of 60%, was normal. Amlodipine-induced edema was suspected, and after a short course of diuretics, the edema resolved within a week. Due to suboptimal blood pressure control, the patient was initiated on cilnidipine at a follow-up visit. However, within 2 weeks, he developed pedal edema again, necessitating discontinuation of cilnidipine. He was switched over to prazosin and telmisartan.

Case 5 : Guilty As Charged

A 46-year-old female, known case of TB uveitis, was on anti-tuberculosis treatment (ATT) and was newly diagnosed with hypertension. She was started on cilnidipine monotherapy to minimize potential drug interactions with anti-TB medications. Blood pressure control was achieved within 72 hours of initiating cilnidipine. However, after 2 months, she developed bilateral pedal edema. Liver, kidney, and cardiac functions were normal. A pulmonologist initially suspected rifampicin-induced edema, and a diuretic was administered, but the edema persisted. The patient was then referred to the Medicine OPD, where cilnidipine was suspected to be the cause of the edema. Cilnidipine was discontinued, and the edema promptly resolved within 10 days.

Case 6: An Optimistic Comeback

A 59-year-old male medical professional with a history of hypertension was initially on a fixed-dose combination (FDC) of metoprolol and telmisartan. Due to suboptimal blood pressure control, he was switched to a combination of metoprolol, telmisartan, and cilnidipine. Nine months after starting cilnidipine, he developed slowly progressive pedal edema, despite normal cardiac, liver, renal, and thyroid function.

He was switched to an FDC of chlorthalidone (6.25 mg), metoprolol, and telmisartan, which resolved the edema but led to suboptimal blood pressure control. To manage his blood pressure more effectively, cilnidipine was reintroduced at a reduced dose of 2.5 mg, alongside the previous FDC, resulting in stable blood pressure without recurrence of edema.

DISCUSSION

Calcium channel blockers (CCBs), particularly dihydropyridines such as cilnidipine and amlodipine, are frequently used to manage hypertension. However, a common adverse effect associated with CCB therapy is peripheral edema, especially pedal edema. This case series illustrates cilnidipine-induced pedal edema in patients with various comorbidities, including hypertension, diabetes, and cerebrovascular disease.

The mechanism behind CCB-induced edema involves vasodilation of pre-capillary arterioles without corresponding dilation of venules, leading to increased hydrostatic pressure and fluid leakage into the interstitial space [5]. Although cilnidipine is thought to have a lower incidence of edema due to its N-type calcium channel blockade [6], our cases indicate that it can still cause edema, particularly at higher doses or in susceptible patients.

Observations from this series reveal variability in the onset of edema, with some patients developing it within weeks and others after months of therapy. Discontinuation or dose reduction of cilnidipine often led to resolution of edema, supporting the role of dose-dependence [7]. Notably, in Case 6, a lower dose of cilnidipine (2.5 mg) did not cause recurrence of edema, underscoring the importance of individualized dose titration [8]

The alternative use of benidipine in Case 3 suggests an alternative in preventing recurrent edema. Benidipine's balanced action on afferent and efferent arterioles may effectively lower capillary hydrostatic pressure, making it a potential alternative for patients prone to CCB-induced edema. [9] This case series highlights the need for vigilant monitoring of side effects in patients on CCBs, especially those with additional risk factors such as diabetes or renal impairment. Our case 2 also underscores the potential for cilnidipine-induced edema to lead patients to seek diuretics for relief, while also highlighting the risk of diuretic therapy causing complications such as hyponatremia, which can pose significant health risks. Further research is essential to clarify the mechanisms of CCB-induced edema and develop strategies to mitigate this common side effect.

CONCLUSION

In conclusion, our case series highlights the significant incidence of pedal edema associated with clinidipine use in patients undergoing treatment for hypertension. While clinidipine is effective in managing blood pressure, the dose-dependent nature of this adverse effect warrants careful monitoring and patient education. Clinicians should be aware of this potential side effect and consider individualized treatment plans, including dose adjustments or alternative therapies, to mitigate discomfort while ensuring optimal blood pressure control.

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