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CASE REPORT

Peripheral Oedema due to S-Amlodipine – A Report of Three Cases

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ABSTRACT

S-amlodipine is a stereoisomer of Amlodipine, a dihydropyridine Calcium Channel Blocker (CCB) used in angina and hypertension. This drug is expected to produce a lesser incidence of pedal oedema, as compared to Amlodipine, based on the limited data available from clinical trials. However, conflicting results have been noted with this drug, in relationship to the occurrence of pedal oedema. We report three cases, where the patients either did not recover from pedal oedema, or had a worsening of pedal oedema after substituting S-amlodipine in place of other CCBs that caused pedal oedema.

Introduction

Amlodipine is a dihydropyridine Calcium Channel Blocker (CCB) approved by the United States Food and Drug Administration (US FDA) for the management of angina (both stable and unstable) and hypertension. Amlodipine has been available in Nepal since a long period, and is used widely. Recently, the enantiomer of Amlodipine (S-amlodipine) has been approved by the Department of Drug Administration (DDA), Kathmandu, the drug regulatory authority of Nepal, and has been marketed. We noted peripheral oedema in a few patients being treated with S-amlodipine, which contradicts the claims made by the trials carried out on S-amlodipine. In this short communication, we report three cases of pedal oedema associated with the use of S-amlodipine, and share our opinion regarding the use of S-amlodipine over Amlodipine.

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Case Vignette 1

A 65 year old male patient, diagnosed to have hypertension for the past three years, was on irregular medications, and also had chronic daily headache. He was prescribed Tab. Propranolol for migraine prophylaxis. For hypertension, he was started on Tab. Amlodipine at a dose of 5 mg once daily, which was increased to 10 mg once daily, during subsequent visits. After 10 months of Amlodipine therapy, the patient presented to the medical Out-Patient Department (OPD) of Manipal Teaching Hospital (MTH) with swelling of the extremities, and abdominal distension. His routine examination results, renal function, and cardiac status were normal. Pedal oedema, a known side effect of Amlodipine, was attributed to the drug. Since S-amlodipine is considered as an alternative 'switch over drug' in patients developing pedal oedema due to amlodipine, the patient was started on Tab. S-amlodipine 10 mg, once daily. However, after introduction of S-Amlodipine, the swelling further increased, as noted on the next followup (one month later). Following the increase in pedal oedema, Tab. S-amlodipine was stopped

and the patient was started on Tab. Enalapril 10 mg once daily, after which the swelling subsided completely.

Case Vignette 2

A 42 year old female patient, a diagnosed case of hypothyroidism and hypertension on Tab. Levothyroxine 100 mcg and Tab. Nifedipine 20 mg twice daily, presented to the medical OPD of MTH with swelling of both lower limbs. Since the swelling developed after Nifedipine therapy, and investigations including urine (routine and microscopy), serum creatinine, and serum albumin were normal, and the patient did not have any features of Congestive Heart Failure (CHF), Nifedipine-induced pedal oedema was suspected. Nifedipine was stopped, and the patient was put on Tab. Enalapril 5 mg once daily initially, and was increased to 10 mg, once daily. In spite of Enalapril therapy, the BP was not controlled, and the patient was started on Tab. S-amlodipine, as it is known to cause less of pedal oedema, and is considered an ideal drug for switch over therapy for the patients developing pedal oedema with the use of CCBs. The severity of the pedal oedema further increased on the next follow-up, and therefore Tab. S-amlodipine was stopped and the patient was started on Tab. Losartan 50 mg once daily, with good control of BP. The pedal oedema subsided completely.

Case Vignette 3

A 36 year old female patient was started on Tab. Amlodipine 5 mg once daily, for the last two months. She was a known hypertensive for the past 4 years, but was not previously on medication. After 3 months of therapy with Amlodipine, the patient developed swelling of limbs, and the distension of the abdomen. A diagnosis of pedal oedema due to Amlodipine was made after excluding other causes, and the patient was switched over to Tab. S-amlodipine 5 mg once daily, following which the swelling further increased. Routine investigations and thyroid function tests were normal. There were no symptoms of CHF. S-amlodipine was stopped, and Tab. Enalapril 5 mg was started, once daily. The pedal oedema subsided on stopping S-amlodipine.

Discussion

Amlodipine is a 1,4- dihydropyridine derivative CCB, which is structurally related to Felodipine, Nifedipine, and Nimodipine. Unlike other currently available CCBs in the dihydropyridine class, amlodipine has a long duration of action [1]. It is approved for use in hypertension and angina. Because of its better safety profile, convenient once daily dosing etc, it is one of the preferred antihypertensive agents. However, it is known to cause Adverse Drug Reactions (ADRs) such as abdominal pain, nausea, palpitation, flushing, head ache, dizziness, sleep disturbances etc [2]. Among the various ADRs, peripheral oedema (swelling of ankles and feet) may necessitate a change in drug therapy during Amlodipine treatment. This ADR is found to be dose dependent, with incidence of 1.8 -10.8% on a dose between 2.5 to 10 mg, daily. A higher prevalence of pedal oedema was observed in women, than in men [3].

Amlodipine is a 1:1 mixture of R and S enantiomers. Various studies on the racemic mixture of (R) and (S) isomers, have shown that the S (-) isomer of Amlodipine has a greater pharmacological effect. Studies on amlodipine as a displacement of (3H) (-) PN 200-110 binding, showed that displacement was stereoselective, with the S (-) isomer being 1000 times more potent than the R (+) isomer [4]. The S-enantiomer has 1000 times more potent affinity for the dihydropyridine receptor than the R-isomer [5]. The S-isomer has also got a longer half-life (49.6 hours) than the R-isomer (34.9) or the recemate (44.2 hours) [6]. Based on these observations, it is believed that the use of isolated S-amlodipine, the pharmacologically active isomer of amlodipine, instead of the racemic mixture, could be of immense benefit as the required dose and systemic toxicity can be reduced [7].

During our literature survey, we could locate only two clinical trials conducted on S-amlodipine. One double blind, double dummy, randomized, comparative clinical trial, compared the efficacy and tolerability of 2.5 mg of S-amlodipine with 5 mg of Amlodipine in the treatment of mild to moderate hypertension. Two hundred out patients (97 women and 103 men) with a mean age of 53.4 ± 5.58 years, with stage I and stage II hypertension were enrolled in the study. Ninety seven patients in the S-amlodipine 2.5 mg treatment group and 91 patients in the Amlodipine 5 mg treatment group completed the study. The study concluded that S-amlodipine 2.5 mg is equivalent in its efficacy and tolerability when compared to Amlodipine 5

mg in the treatment of mild to moderate hypertension [7].

Another study was the Post Marketing Surveillance (PMS) study on S-amlodipine, and evaluated the efficacy and tolerability of S-amlodipine (2.5/5 mg) in patients with hypertension. A total of 1859 patients (743 women and 1116 men) were enrolled in 359 different centers in India. The study concluded that S-amlodipine 2.5/5.0 mg is found to be effective and well tolerated in the treatment of hypertension, and is an ideal switch over therapy for patients having peripheral oedema with conventional amlodipine [8].

The drug was approved by the DDA, Kathmandu, and is available in Nepal. Based on the available data, the drug was approved for availability by the Drug and Therapeutics Committee (DTC) [9] of our hospital. In patients developing pedal oedema with conventional Amlodipine, S-amlodipine is prescribed as the switch over therapy, as recommended by the PMS study [8]. We found the results contradictory to that reported in the clinical trial, during our use of S-amlodipine.

One patient (case vignette 1) developed pedal oedema, following which we stopped Amlodipine and started S-amlodipine at the same dose. But the pedal oedema worsened further, and S-amlodipine was stopped. But immediately after stopping S-amlodipine, the pedal oedema subsided, suggesting that the drug may not be a 'switch over drug' for patients developing pedal oedema with Amlodipine.

In case vignette 2; The patient developed pedal oedema with Nifedipine, and was started on the ACE inhibitor Enalapril. However, BP was not controlled, and hence S-amlodipine was started. After starting S-amlodipine, the pedal oedema further increased necessitating stoppage of the drug. After stopping S-amlodipine, the patient's pedal oedema improved dramatically. This report suggests that S-amlodipine may not be an alternative, even for patients developing pedal oedema due to CCBs other than S-amlodipine. In the other patient (case vignette 3), again the patient developed pedal oedema with conventional amlodipine, due to which she was switched on to S-amlodipine, which led to an increase in the pedal oedema.

These reports raise a pertinent question in our mind whether there is a need for marketing drugs which lacks sufficient evidence on the efficacy and the adequate safety data. We could not locate the safety profile of this drug during our literature survey, that included the commonly used drug information sources *Martindale Extra Pharmacopoeia, United States Pharmacopoeia, Drug Information for the Healthcare Professional (USPDI), British National Formulary (BNF), Micromedex electronic source of drug information, Pubmed, Scholar Google, Google* etc. Moreover, to the best of our knowledge, this drug is not approved by the drug regulatory authorities of any developed country, and the entire spectrum of claims made for so called 'chiral molecules', are not justified totally. If this issue is not taken care properly, Nepal may become the market for several chiral molecules like S-atenolol, R-ondansetron, L- salbutamol, S-metoprolol, S-pantoprazole, L-cetirizine etc, at a point in time, where we are devoid of essential medicines in Nepal.

Conclusion

The association of pedal oedema due to S-amlodipine has alerted us to begin generating safety data of drugs on our own population, rather than relying on the data generated from the foreign population, which may vary significantly with regard to genetic make up, diet, lifestyle etc. Clinicians have a responsibility to monitor the patients on drugs like S-amlodipine, which do not have adequate safety and efficacy data. Since our observations are based on only three cases, there is a need for more data to confirm our findings. The study needs be continued, for us to draw any major conclusions.

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