REVIEW ARTICLE

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Ankle Oedema and Sympathetic Activation

Roberto Fogari

Department of Internal Medicine, University of Pavia, Pavia, Italy

Abstract

Ankle oedema is a common adverse event during treatment with dihydropyridine (DHP) calcium channel antagonist therapy, the incidence of which is dose related. The three mechanisms put forward to explain the formation of oedema during calcium channel antagonist therapy are arteriolar vasodilation, impairment of the local vascular autoregulation of blood flow and impaired protection against hydrostatic load. The importance of differential arteriolar-venular dilation has been demonstrated in numerous clinical studies. In particular, differences in sympathetic overactivation after arterial vasodilation have been shown to be related to differences in ankle oedema rates. If these results are confirmed, calcium channel antagonists that activate the sympathetic nervous system to a lesser extent, such as manidipine, may become first-choice calcium channel antagonists because of their more favourable adverse event profile.

1. Introduction

Ankle oedema has been considered the most common side-effect of dihydropyridine (DHP) calcium channel antagonist therapy. Approximately 15 years ago, Opie[1] reported that this adverse event occurred in 1–15% of patients. It is now widely accepted that the incidence of ankle oedema is dose dependent. In one study the reported incidence of ankle oedema in amlodipine and felodipine recipients was 5% in patients receiving 5 mg/day and 25% when the dosage of either drug was 20 mg/day.[2]

2. Clinical Characteristics of Ankle Oedema

Ankle oedema is characterised clinically by diffuse swelling of the affected area. It is one of the most frequent side-effects reported by patients receiving calcium channel antagonists, with an incidence ranging from 5% for verapamil and 6% for manidipine to 22% for amlodipine and 29% for nitrendipine.[3,4] Oedema induced by calcium channel antagonist therapy is most prominent during the evening and resolves overnight,[5] and is more common in women than in men.[3] It is not associated with an increase in body weight and is not accompanied by sodium retention. Ankle oedema persists during DHP treatment, and may become more severe during long-term therapy. In the majority of patients, DHP calcium channel antagonist-induced ankle oedema is relatively mild. However, it can still lead to the discontinuation of therapy and poor patient compliance,[3] which is not helpful when trying to achieve blood pressure lowering goals.

3. Quantification of the Oedematigenous Potential of Calcium Antagonists

At present there are two possible methods for quantifying the oedematigenous potential of

calcium channel antagonists. The first is the evaluation of foot-ankle volume. This is based on the principle of water displacement, which usually involves placing the foot and ankle in a water bath and then evaluating the change in volume.

Van Hamersvelt and colleagues[6] used a new, indirect and precise method for measuring foot volume to evaluate the effect of the acute administration of oral nifedipine 20mg on foot volume and sodium excretion in healthy volunteers. Placebo, oral captopril 25mg and intravenous diazoxide 150mg were used as comparators. Compared with placebo, diastolic blood pressure was significantly reduced by nifedipine for up to 60 min post-dose, by captopril for at least 80 min post-dose and by diazoxide for only 30 min post-dose. No change in foot volume was observed after the administration of captopril and diazoxide compared with placebo. In contrast, there was a significant increase in foot volume over the 3-hour study period after nifedipine. Fractional sodium excretion was reduced by placebo and diazoxide, but increased after nifedipine and captopril. On the basis of these findings, the investigators concluded that the nifedipine-induced increase in foot volume was not related to water or salt retention.

Water displacement volumetry was also used by Lund-Johansen et al.,[7] who evaluated the increase in ankle volume after long-term therapy with the DHP calcium channel antagonists amlodipine and lercanidipine; the latter agent has the same lipophilic properties as manidipine. Ankle volume increased from baseline to a significantly greater extent in amlodipine (60.4%) than in lercanidipine (5.3%) recipients. In addition, the number of patients with evidence of oedema on physical examination, and with symptoms of leg swelling or leg heaviness was significantly higher in the amlodipine group. These findings were supported by the results of a study by Pedrinelli et al.,[8] which showed once again that ankle volume was increased more markedly by amlodipine than lercanidipine.

Additional data supporting the reduced potential of lipophilic DHP calcium channel antagonists to induce ankle oedema were reported by Tikhonoff et al.[9] Their study showed that increases in ankle volume with manidipine or lercanidipine were small. The 6.6% increase seen in lercanidipine recipients was similar to that reported in the study by Lund-Johansen et al.[7]

The second method of quantification is by the evaluation of pretibial subcutaneous tissue pressure (PSTP), which is performed by connecting the ankle subcutaneous interstitial environment to a water manometer.

This is facilitated by introducing a needle into the subcutaneous tissue, which is connected to a water manometer via a capillary tube; both the tube and the manometer are filled with saline solution. The movement of the saline solution can be balanced using a micropump, which allows movement of 1mm Hg of water pressure, enabling equilibrium to be attained. Subcutaneous tissue pressure can then be assessed. If subcutaneous pressure is negative, as is often the case in elderly patients, the meniscus of the saline solution moves in the direction of the patient. Conversely, positive subcutaneous pressure results in the meniscus of the saline solution moving slightly in the direction of the observer. However, this technique is not widely used because it is invasive and quite complex.

Nevertheless, Fogari et al.[10] used PSTP to evaluate the effect of long-term therapy with six DHP calcium channel antagonists (amlodipine, nifedipine, felodipine, isradipine, manidipine and lacidipine) in hypertensive patients. PSTP increased from baseline by 33, 30, 27, 25, 20 and 18% in the amlodipine, nifedipine, felodipine, isradipine, manidipine and lacidipine groups, respectively ($P < 0.001$ for the first four agents and $P < 0.01$ for manidipine and lacidipine). The increase in PSTP in all treatment groups was not related to the clinical presence or absence of oedema. The investigators suggested that differences in the potential to cause oedema could be due to differences in pharmacological properties of the studied agents, such as vascular selectivity, lipophilicity and volume of distribution.

The oedema index, which takes into account both PSTP and ankle volume, was also assessed in these patients. Similar to the reported results for

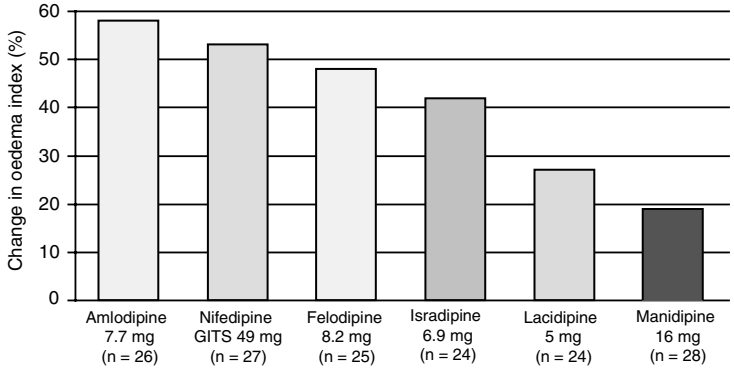

Fig. 1. Effect of 8 weeks of treatment with different calcium channel antagonists on oedema index in hypertensive patients.[9] Oedema index = % subcutaneous tissue pressure + % ankle volume.

PSTP, the oedema index increased in all treatment groups, but there was marked interagent variability. With amlodipine and nifedipine, the increase from baseline was greater than 50%, whereas the increase was smaller with lacidipine and manidipine (32 and 28%, respectively) (figure 1).

4. Mechanisms of Calcium Channel Antagonist-induced Oedema Formation

Three mechanisms have been postulated to be involved in the formation of oedema during DHP calcium channel antagonist therapy,[11] all of which lead to an increase in capillary hydrostatic pressure, which in turn results in transcapillary fluid loss.

4.1. Arteriolar Vasodilation

Messing et al.[12] reported that the major sites of action of the calcium channel antagonists verapamil, nifedipine and felodipine were the small precapillary arterioles. In their experiment in spontaneously hypertensive rats, all three calcium channel antagonists significantly increased the diameter of arterioles, with the most marked effects observed in the smallest arterioles; no changes in venular diameters were observed. These results indicate that there is a greater decline in arteriolar than in venular resistance during calcium channel antagonist therapy.

Furthermore, a study of felodipine in healthy volunteers concluded that increased capillary pressure, secondary to vasodilatory effects, was partly responsible for the oedema formation induced by felodipine and other DHP calcium channel antagonists.[5]

4.2. Impairment of Local Vascular Autoregulation of Blood Flow

Additional data from the above study by Messing et al.[12] showed that a low dose of felodipine (10 μg/kg) slightly decreased blood pressure, slightly dilated the largest arterioles and stopped the spontaneous vasomotion of the smallest arterioles. A 30 μg/kg dose of felodipine induced a greater decrease in blood pressure, a greater increase in the diameter of the largest arterioles, and both a cessation of the spontaneous vasomotion and an increase in the diameter of the smallest arterioles. This could explain the second proposed mechanism, the impairment of spontaneous autoregulation of blood flow during treatment with a calcium channel antagonist.

Gustafsson et al.[5] also concluded that interference with local vascular control is one of the actions of felodipine that could contribute to oedema formation, along with increased capillary pressure. These researchers performed one of the first studies in humans to evaluate the effects of a calcium channel antagonist on microvascular

parameters. They demonstrated that felodipine increased both forearm blood flow and cutaneous blood flow, and caused a net transcapillary fluid filtration from blood to tissue secondary to an increase in hydrostatic pressure. Hydrostatic pressure was increased as a result of more pronounced vasodilation in pre versus post-capillary vessels. The investigators also reported that the decrease in diastolic blood pressure induced by felodipine was accompanied by an increase in venous pressure. Felodipine thus seemed to increase the difference between arteriolar and venular dilation, as a result of venular constriction.

4.3. Impaired Protection Against Hydrostatic Load

Impaired protection against hydrostatic load because of impairment of the myogenic precapillary sphincter constriction has been suggested as a potential mechanism of ankle oedema.

Gustafsson et al.[5] suggested that calcium channel antagonists impaired the vasoconstrictor mechanism involved in oedema prevention under conditions of increased hydrostatic pressure. However, other data suggest that this mechanism does not contribute to the potential for DHP calcium channel antagonists to induce ankle oedema.[9]

5. Importance of Differential Arteriolar-Venular Dilation

The rapid onset of vasodilatory effects is likely to be associated with activation of the baroreflex, causing activation of the sympathetic nervous system and associated increases in plasma norepinephrine levels. Venules in particular are very

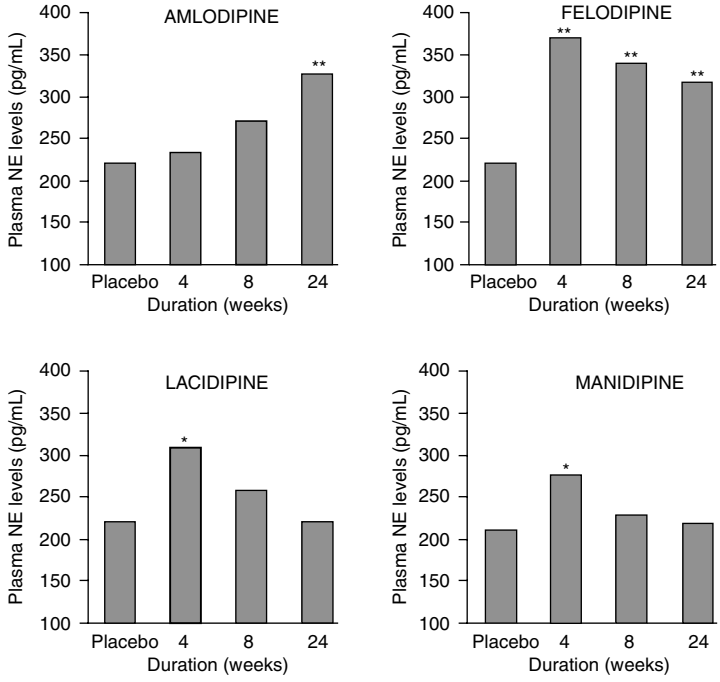

Fig. 2. Effect of 24 weeks of treatment with amlodipine 5–10 mg/day, felodipine 5–10 mg/day, lacidipine 4–6 mg/day and manidipine 10–20 mg/day on plasma norepinephrine plasma levels in hypertensive patients.[12] **NE** = Norepinephrine. $^{*}P < 0.05$; $^{**}P < 0.01$ versus placebo.

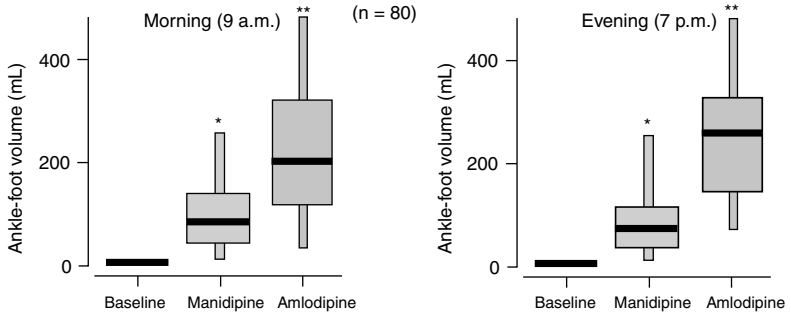

Fig. 3. Effects of 16 weeks of treatment with manidipine 20 mg/day and amlodipine 10 mg/day on ankle-foot volume change in the morning and in the evening. $^{*}P < 0.05$; $^{**}P < 0.01$ versus baseline.[13]

sensitive to norepinephrine because of the presence of α-adrenergic receptors.

The effects of different calcium channel antagonists on reactive activation of the sympathetic nervous system were investigated by Fogari et al.[13] in a study that compared the effects of amlodipine, felodipine and the newer, lipophilic DHP, manidipine and lacidipine, on plasma norepinephrine levels in patients with essential hypertension.

After 24 weeks of treatment in patients with moderate hypertension, both amlodipine and felodipine induced a significant increase in plasma norepinephrine levels; the increase with amlodipine was gradual and only became statistically significant at 24 weeks, whereas the increase with felodipine was rapid and was significant versus baseline after 4, 8 and 24 weeks of therapy. With lacidipine and manidipine there was a transient increase in plasma norepinephrine levels that was significant compared with baseline only at 4 weeks after start of therapy (figure 2).

Another study by Fogari and colleagues[14] combined measurements of sympathetic activation and ankle oedema parameters. The agents studied in the randomised, crossover trial were amlodipine (the DHP with the greatest potential to cause oedema) and the new lipophilic DHP agent, manidipine; there was a 4-week placebo run-in period at baseline and a 4-week placebo wash-out

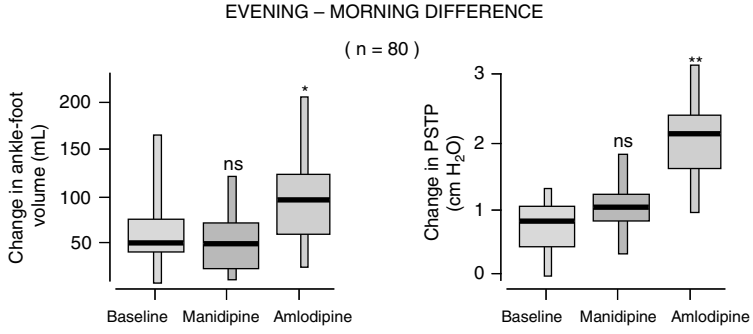

Fig. 4. Effect of gravity (standing) on volume and pretibial subcutaneous tissue pressure changes during 16 weeks of treatment with manidipine 20 mg/day or amlodipine 10 mg/day.[13] **ns** = Not statistically significant; **PSTP** = pretibial subcutaneous tissue pressure. $^{*}P < 0.05$; $^{**}P < 0.01$ versus baseline.

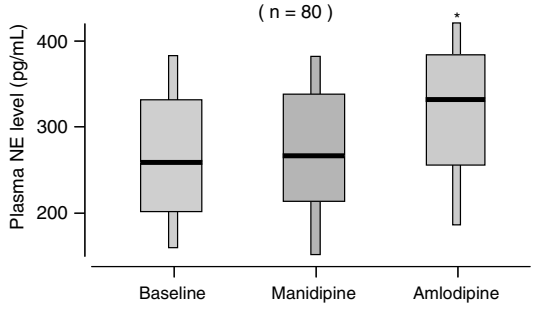

Fig. 5. Plasma norepinephrine levels during 16 weeks of treatment with manidipine 20 mg/day or amlodipine 10 mg/day.[13] **NE** = Norepinephrine. $^{*}P < 0.05$ versus baseline.

period between treatments. Compared with amlodipine, manidipine was associated with smaller increases in the morning and evening ankle volume from baseline values (figure 3). The results for PSTP were qualitatively similar. The effect of daytime standing and gravity could be determined by looking at the evening versus the morning measurements for ankle volume and PSTP. With manidipine, the increases in these parameters over the course of the day were similar to those during the placebo period, indicating that standing did not influence the effects of manidipine on ankle volume and PSTP. Conversely, both these parameters increased from baseline values over the course of the day during amlodipine treatment (figure 4). Plasma norepinephrine levels were not significantly altered during the 16-week manidipine treatment period, but significantly increased from baseline values during amlodipine treatment period (figure 5). There was significant positive correlation between changes in plasma norepinephrine levels and both PSTP and ankle volume during amlodipine therapy, particularly in the morning; this was not the case during manidipine therapy.

6. Conclusions

Ankle oedema in patients treated with DHP calcium channel antagonists seems to be related to sympathetic overactivation after arterial vasodilation. DHPs such as manidipine appear to activate the sympathetic nervous system to a significantly lesser extent than other agents in this class. From a theoretical point of view this reduction of sympathetic tone could also contribute beneficial effects in reducing damage to other target organs, including the kidney, the coronary arteries, the large arteries and possibly, the cerebral vasculature. Therefore these types of drugs should be considered as a first-choice therapy.

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Correspondence and offprints: *Roberto Fogari*, Department of Internal Medicine, University of Pavia, Pavia, Italy.
E-mail: r.fogari@smatteo.pv.it