Pedal Edema—Not All Dihydropyridine Calcium Antagonists Are Created Equal

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The COHORT study headed by Leonetti and a well-known group of Italian investigators provides us with conclusive and yet provocative data regarding a common adverse effect of dihydropyridine calcium antagonists, namely, pedal edema. In this multicenter, double blind, parallel group study of more than 800 elderly patients, amlodipine had a significantly (P < .001) higher rate of pedal edema (19%) compared with lercanidipine (9%) and lacidipine (4%). The dropout rate because of edema and edema-related symptoms was again significantly higher in the amloidipine than in either the lercanidipine or lacidipine group. The intensity of edema tended to be milder in lercanidipine patients compared with amloidipine and lacidipine. Of note, blood pressure (BP) was equally and effectively controlled in all three treatment groups. These thorough observations would indicate that for any given fall in BP, the incidence of vasodilatory edema was significantly less with “membranophilic” calcium antagonists such as lercanidipine and lacidipine compared with the second-generation calcium antagonists amloidipine, nifedipine, felodipine, and isradipine.

Pedal edema is one of the most common adverse effects of calcium antagonists. It has been observed with all available dihydropyridine agents, but it also seems to occur to a lesser extent with verapamil and diltiazem. The incidence of pedal edema is clearly dose dependent and may exceed 80% with very high doses of dihydropyridine calcium antagonists. With starting doses of amloidipine or felodipine, only about 5% of patients will complain of swelling of the feet or ankles. Of clinical interest is the observation in the COHORT study that the incidence of edema gradually increased throughout the study (despite the fact that the calcium antagonist dose was kept constant after 8 weeks) to reach the highest levels at the end of the study in all three calcium antagonist arms. This clearly indicates that pedal edema is not transient (ie, will not go away with time) but, if anything, becomes more severe with continued calcium antagonist therapy.

Pedal edema is not associated with salt and water retention, as dihydropyridine calcium antagonists have been shown to be natriuretic. It therefore does not respond well to diuretic therapy. In susceptible patients with pedal edema, capillary permeability may increase to the extent that erythrocytes are leaked from the capillary into the interstitium and cause a petechial rash with prolonged exposure to calcium antagonists. The petechial rash can lead to hyperpigmentation and discoloration in the edematous area (Fig. 1).

The four main determinants of the capillary fluid filtration into the interstitium are: 1) intracapillary pressure, 2) interstitial oncotic pressures, 3) capillary permeability, and 4) lymphatic drainage. With change from the supine to the standing posture, capillary fluid filtration is held constant by the venoarteriolar reflex, causing postural vasoconstriction in both the arteriolar and the venous limb. The precapillary vasoconstriction is selectively diminished by calcium antagonists. As a consequence of attenuated arteriolar constriction, intracapillary pressure rises. Capillary hypertension will lead to a net capillary fluid filtration into the interstitium. Thus, gravitational factors clearly have a permissive role in promoting or favoring pedal edema formation with calcium antagonists. Calcium antagonists seem to block the myogenic component of the reflex control of skin blood flow, which is independent of neural, metabolic, and other hormonal influences.

As attenuation of postural vasoconstriction seems to be a nonspecific feature of calcium antagonists, why is it, then, that for a given degree of vasodilation (antihypertensive efficacy) are there differences from one drug to another? Experimental data have shown that in contrast to traditional dihydropyridine calcium antagonists, which predominantly dilate the afferent arteriole in the kidney, lercanidipine also has a distinct effect on the efferent arteriole. Thus, lercanidipine provides a more balanced pre- and postglomerular dilation. Such a balanced vasodilator conceivably could take place in other capillary beds as well, thereby reducing capillary hypertension and lessening pedal edema. The newer calcium antagonists such as lercanidipine differ from traditional drugs in that they have sustained access to the site of action by residing in the cell membrane and also have a long receptor half life (Fig. 2).
Because pedal edema with calcium antagonists is caused by capillary hypertension during upright posture, it stands to reason that a drug that would normalize intracapillary pressure should diminish this edema. Capillary hypertension can be reduced by venous dilation, and both angiotensin converting enzyme inhibitors (ACEIs)\textsuperscript{3} as well as angiotensin receptor blockers have been shown to counteract the effect of calcium antagonists in this regard.

We should not forget that even in the COHORT study, a number of patients on lercanidipine still presented with pedal edema, although the incidence was lower than in patients on amlodipine. Thus, the combination of an ACEI or an angiotensin receptor blocker with lercanidipine is bound to be useful in clinical practice.

The take-home messages for the practicing physician from the COHORT study are simple and straightforward. First, for a similar fall in BP, lercanidipine, a new membrandophilic calcium antagonist, produces less pedal edema than does amlodipine. Second, a lesser incidence of pedal edema may be due to lercanidipine’s venular dilating effect, which decreases capillary hypertension and transcapillary fluid exudation. Third and finally, even with lercanidipine, pedal edema will remain an issue in susceptible patients, and combination therapy with either an ACEI or an angiotensin receptor blocker might be appropriate.

References


