CONCEPTS IN HYPERTENSION

A Journal Article-Based Approach to Understanding the Clinical Aspects of Hypertension

Volume 2 Issue 12 December 2017

## Article of Interest

Gradman, A et al. Combined Enalapril and Felodipine Extended Release for Systemic Hypertension. American Journal of Cardiology. 1997. (Click to Access)

## Context and Study Objective

Calcium channel antagonists (CCBs) are widely used anti-hypertensives but peripheral edema can limit their use. While the primary endpoint of this study was the anti-hypertensive efficacy of combination CCB/angiotensin converting enzyme inhibitor (ACEi) therapy versus either as monotherapy, a secondary endpoint was the incidence of CCB-related edema.

## Design, Setting, and Participants

In a placebo-controlled, double-blind fashion, patients were randomized to varying doses of felodipine, enalapril, combination therapy, or placebo for 8 weeks. Peripheral edema was only recorded if volunteered by the patient. Those with heart failure, liver or chronic kidney disease were excluded.

## Results

| Edema Incidence by Treatment Group | | | |
|---|---|---|---|
| | Placebo | Felodipine | Felodipine & Enalapril |
| Edema | 1.3% | 10.8% | 4.1% |

-700 participants were included with a mean age of 54. 65% were men; 80% were white. Baseline blood pressure was 155/102 mm Hg.

-The incidence of felodipine induced edema was dose-dependent. The mean frequency was 11% when low, medium, and high-dose therapy were considered in aggregate. Rates of edema by CCB dose were not reported.

-Among those on combination CCB/ACEi therapy, edema rates declined by two-thirds.

## Clinical Perspective

-I pair amlodipine with an ACEi or angiotensin receptor blocker (ARB). While more evidence exists for the addition of an ACEi, I favor ARBs as the incidence of cough is markedly lower. Low-dose combination therapy reduces side-effect burden; both amlodipine-olmesartan and amlodipine-benazepril combination tablets are available.

-More broadly, edema should not be an indication for CCB withdrawl. Since edema is dose-dependent, lowering the dose is effective. Third generation agents such as amlodipine or non-dihydropyridine CCBs such as diltiazem and verapamil are also less edema-genic than 2nd generation agents like nifedipine and felodipine. Since the edema is not related to volume retention, diuretics are of little benefit.

-Mechanistically, CCB-associated edema is not the result of fluid retention. Rather, CCBs decrease arteriolar resistance which increases the arteriolar-venous pressure gradient at the level of the capillary. This change in hydrostatic forces favors the extravasation of fluid from the vascular to the interstitial space. Because ACEi therapy promotes venodilatation, the transcapillary pressure gradient is normalized and extravascular fluid leak is minimized.

-Study Criticism: this paper underestimates the incidence of CCB-related edema as self-report rather than active surveillance was employed. Other studies indicate rates as high as 25% on full dose therapy.

-Disclosures: I have no conflicts to declare.


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