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Evolution of Calcium Antagonists: Past, Present, and Future

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Summary: Calcium antagonists were originally introduced as fast-acting vasodilators exhibiting powerful antihypertensive properties. They have now evolved into agents exhibiting a smooth onset and a long duration of action. Early agents, because of their rapid onset of action, were associated with a host of compensatory hemodynamic adverse effects including cardioacceleration and sympathetic stimulation. In contrast, the newer agents appear to retain the antihypertensive properties, but with an improved tolerability profile. Across the cardiovascular disease continuum, the presence of diabetes adds to the risk for cardiovascular events. In diabetic patients with hypertension, multiple drug therapy is clearly indicated. Agents such as calcium antagonists that normalize hemodynamics in this patient population might be expected to demonstrate beneficial effects on mortality. Evidence from the Systolic Hypertension in Europe and the Systolic Hypertension in China trials demonstrated over a 50% reduction in total mortality in the diabetic subgroup in patients treated with calcium antagonists. Among the calcium antagonists, particularly among the dihydropyridine subclasses, the efficacy of the drugs has been accompanied by some side effects, in particular pedal edema. The incidence of pedal edema is dose dependent and is the result of vasodilation and intracapillary hypertension. Newer calcium antagonists demonstrate antihypertensive efficacy similar to that of their predecessors but appear to have a reduced propensity to cause edema.

Key words: antihypertensive agents, calcium antagonists, hypertension, lercanidipine, diabetes, pedal edema

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Introduction

Evidence-based medicine, which can be defined as the conscientious and judicious use of the best, current clinical research evidence, is the widely accepted basis for therapy decisions today. Accordingly, physicians must be aware of new scientific developments and their impact on clinical practice. However, not all evidence is created equal, and there exists a distinct hierarchy. It is exemplified by integral information, which is information that could be available for use of angiotensin-converting enzyme (ACE) inhibitors in congestive heart failure (CHF). These include numerous prospective, randomized trials, pathophysiologic studies, and various meta-analyses, all of which, in unison, attest to the safety and efficacy of ACE inhibitors in CHF.

In hypertension, as elsewhere, the standard of reference of evidence-based medicine is the multicenter, randomized, prospective trial designed to test the safety and efficacy of an antihypertensive drug. The Systolic Hypertension in Europe (Syst-Eur) trial, a very thorough, prospective, randomized, double-blind trial in isolated systolic hypertension, was conducted with more than 4,000 elderly patients, but was prematurely terminated because there was a 42% reduction in the stroke rate of the active treatment group relative to the placebo arm ($p = 0.003$).[1, 2] Based on this study, the Joint National Committee (JNC) labeled long-acting dihydropyridine calcium antagonists as an appropriate alternative (to diuretics) in elderly patients with isolated systolic hypertension.[3] However, this class of antihypertensive agent has also been the subject of erroneous statements. This is, perhaps, in part due to the diversity within the class. Unlike ACE inhibitors, which share many class effects, the calcium antagonists have gone through an evolution of development beginning with three distinct chemical entities (i.e., verapamil, diltiazem, and nifedipine). These were all originally introduced as fast-acting vasodilators exhibiting powerful antihypertensive properties. However, their fast onset of action was accompanied by a host of compensatory hemodynamic adverse effects including cardioacceleration and sympathetic stimulation, forming the basis for controversy given their effect on cardiovascular outcomes.[4] A second generation of calcium antagonists, including verapamil-SR, nifedipine-XL, and felodipine-ER were developed

with modified release properties to slow onset of action. A third generation was intrinsically long acting. Agents in this third generation with a long plasma half-life, like amlodipine, are washed out from the receptor relatively fast. In contrast, newer agents, while exerting similar 24-h efficacy as do members of the third generation, have a short plasma half-life but a long receptor half-life. These next generation agents include lercanidipine, lacidipine, and manidipine. This evolution in the calcium antagonist class has been aimed at maintaining the antihypertensive properties but improving the tolerability profile.

The Diabetic Hypertensive Patient

Consensus statements and guidelines have, to a large extent, arisen out of evidenced-based medicine analyses. This has been especially true of the hypertensive patient with concomitant diabetes. The National Kidney Foundation, American Diabetes Association, and JNC trials have all focused attention on this important and expanding group of patients. Because these patients carry such a high risk of cardiovascular events, there is little debate that they should be placed on triple therapy including a statin, aspirin, and a blocker of the angiotensin system regardless of the blood pressure level.

When diabetes is coupled to hypertension the risk of total mortality and cardiovascular mortality doubles.[5] The U.K. Prospective Diabetes Study (UKPDS)[6] demonstrated that in the diabetic hypertensive patient it is more important to lower blood pressure than blood sugar. For any diabetes-related endpoint, for death related to diabetes, for all-cause mortality, myocardial infarction, stroke, or microvascular disease, the benefits derived by blood-pressure reduction exceed the benefits of blood-sugar reduction. In contrast to what was taught in medical school, it is more important to normalize hemodynamics than it is to normalize metabolic endocrine findings.

A meta-analysis by Furberg *et al.*[7] created a great deal of unnecessary controversy regarding the use of calcium antagonists by showing that patients with coronary heart disease using short-acting nifedipine had an increase in total mortality. This led to a series of articles[8–10] and commentaries[11] in which investigators suggested that patients with diabetes mellitus on calcium antagonist therapy had an increased risk of cardiovascular complications, especially when compared with patients on ACE inhibitors. However, the evidence from Syst-Eur[12] and the Systolic Hypertension in China (Syst-China)[13] trials demonstrated over a 50% reduction in total mortality in the diabetic subgroup, clearly attesting to impressive benefits of calcium antagonists in these patient populations.[5] The recent findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial have thoroughly and exhaustively established safety and efficacy of the dihydropyridine calcium antagonists, in particular amlodipine, in a large patient population with essential hypertension, one-third of whom were diabetic, African American, and elderly.[14] This trial indicated that calcium antagonists remain a cornerstone in the antihypertensive arsenal for years to come.

Evidence In Left Ventricular Hypertrophy

An important intermediary step in the disease continuum from uncomplicated hypertension to CHF is left ventricular hypertrophy (LVH). From a meta-analysis of 89 double-blind trials, the best monotherapeutic way to reduce LVH appears to be the ACE inhibitors, closely followed by angiotensin-receptor blocker (ARBs), then the calcium antagonists and diuretics, and least efficient, the beta blockers.[15]

However, within this database, studies involving diabetic patients reveal differences. A study comparing nitrendipine to enalapril showed that blood pressure was lowered to about the same extent with both agents; however, after 24 weeks it appeared that nitrendipine did better than enalapril in reducing LVH. This difference was more pronounced at the end of the study after 48 weeks.[16]

The superiority of a calcium antagonist over an ARB in reducing LV mass was also demonstrated in a study comparing the newest generation calcium antagonist, lercanidipine, to losartan in diabetic, hypertensive patients.[17] It is conceivable that in these patients calcium antagonists are better in reducing LVH than are blockers of the renin-angiotensin system. That 1-year treatment with lercanidipine induced a greater LVH reduction than losartan suggests either that nonhemodynamic factors play a role in the reduction of LV mass in the diabetic patient or that calcium antagonists exert a specific effect on the diabetic heart.

Patient Compliance/Therapeutic Tolerability

What is important in the long-term management of patients anywhere along the disease continuum, of course, is adherence to antihypertensive therapy. A study by Elliott consisting of 2,829 patients showed that the relative risk (RR) of discontinuing antihypertensive drugs was actually lowest with the calcium antagonists ($n = 837$; RR = 0.56; 95% confidence interval 0.49–0.64; $p < 0.0001$) and highest with beta blockers ($n = 575$; RR = 1.00; 95% confidence interval 0.88–1.16; p value not significant).[18] Of note, ARBs were not included in this study.

However, one common and troublesome side effect of the calcium antagonists, even among the second generation agents and with the third generation drug amlodipine, is pedal edema. The incidence is clearly dose dependent and is a result of vasodilation. The mechanism can be produced experimentally in rats: as the dose of the calcium antagonist is increased, skin plasma albumin leakage increases. Similarly, the dose response phenomenon has been demonstrated with isradipine in humans. When the dosage is increased from 15 to 20 mg, pedal edema virtually doubles, while the antihypertensive efficacy plateaus.[19]

The same holds true for amlodipine. When the dose of amlodipine is increased from the usual dose of 5 mg to a dose of 10 mg, the incidence of pedal edema reaches 25%.[20] One way to diminish this effect is to add an ACE inhibitor[21] or an

ARB.[20, 22] The pathogenic mechanism is very simple. Arteriolar vasodilation (or diminished arteriolar constriction with upright posture), such as that produced by calcium antagonists, increases intracapillary pressure. Intracapillary hypertension causes fluid to be squeezed out into the interstitial space. When an ACE inhibitor or an ARB is added there is dilation on the venous side; thus, intracapillary pressure falls and the edema is reduced. A second way to diminish edema would be for the calcium antagonist to possess dilatory capabilities on both the afferent and efferent arterioles. This is why the newest generation of calcium antagonists, exemplified by lercanidipine, is stimulating so much interest.

In an open-label, uncontrolled study, patients who were selected because they had adverse events typical of dihydropyridine calcium antagonists (e.g., edema, flushing, headache, dizziness) on amlodipine were switched to lercanidipine and then were rechallenged with amlodipine.[23] The most common side effect in the population on baseline therapy was ankle edema, which was reported in nearly 98% of the patients. When these patients were switched to lercanidipine, the incidence of edema fell to 50%. When they were reexposed to amlodipine, the incidence rose again to 86%.

Fogari *et al.*[24] studied ankle edema in a different way by comparing lercanidipine with nifedipine gastronintestinal therapeutic system (GITS). He measured ankle–foot volume and pretibial subcutaneous tissue pressure. The increase in ankle–foot volume measurements was distinctly lower with lercanidipine than with nifedipine. The same was true of the pretibial subcutaneous tissue pressure. The effects of age add an interesting consideration. Older patients appeared to be more susceptible to the development of pedal edema, possibly because their skin is less elastic. However, when the effects of the two calcium antagonists are compared, the slopes relating vasodilatory edema to age were distinctly different with nifedipine, showing a much steeper slope than lercanidipine (Fig. 1). When the subcutaneous tissue pressure was plotted against the ankle–foot volume, there was a clear-cut separation of the two curves attesting to the higher propensity of nifedipine to cause pedal edema when compared to lercanidipine.

The best evidence of differences in calcium antagonism to cause vasodilatory edema comes from a large, multicenter, double-blind, randomized trial in over 800 patients by Leonetti *et al.*,[25] which is discussed elsewhere in this supplement. The propensity to cause edema was evaluated among three calcium antagonists and again showed lercanidipine at similar antihypertensive efficacy to be superior to amlodipine.

What is further intriguing are the effects of these compounds on the kidney. It is accepted that the beneficial effect of ACE inhibitors on nephroprotection is, at least in part, related to the ability of ACE inhibitors to dilate the efferent glomerular arterioles resulting in decreased intraglomerular pressure and ultimately less glomerular injury. Some other antihypertensive agents, the dihydropyridine calcium antagonists included, have a preferential effect on afferent arterioles. However, Sabbatini *et al.*[26] have shown that not all calcium antagonists act alike. Using a rat model, the newer calcium antagonists lercanidipine and manidipine exhibited a balanced effect on afferent and efferent arterioles, whereas the older calcium antagonist nicardipine dilated only the afferent arterioles (Fig. 2). Ongoing studies will show whether these provocative experimental data can be extrapolated to hypertensive patients (Forest Laboratories, Inc., New York, N.Y., unpublished data).

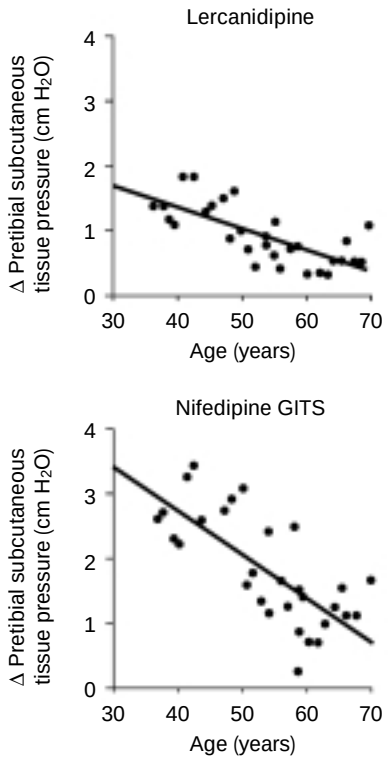

FIG. 1 Increases in pretibial subcutaneous tissue pressure (cm H_2O) caused by lercanidipine 10–20 mg (n = 30) and nifedipine GITS 30–60 mg (n = 30) was reduced with increasing age ($r = -0.74$, $p < 0.01$; $r = -0.72$, $p < 0.01$, respectively). Younger patients who have better tissue integrity and more elastic tissue components may develop tension in the elastic tissue components to counteract fluid filtration from the blood to the interstitial space. GITS = gastrointestinal therapeutic system. Adapted from Ref. No. 24 with permission.

Conclusion

Calcium antagonists as a class represent important and efficacious classes of antihypertensive agents as documented by numerous multicenter, randomized prospective trials. Their utility and popularity is due to their recognized potency as an antihypertensive; moreover, Syst-Eur[1, 2, 12] established the clear superiority of calcium antagonists in the prevention of stroke as well as a clear mortality benefit in hypertensive diabetic patients. As the class continues to evolve, new agents such as lercanidipine demonstrate tolerability advantages over earlier formulations. Also, their ability to dilate both the affer-

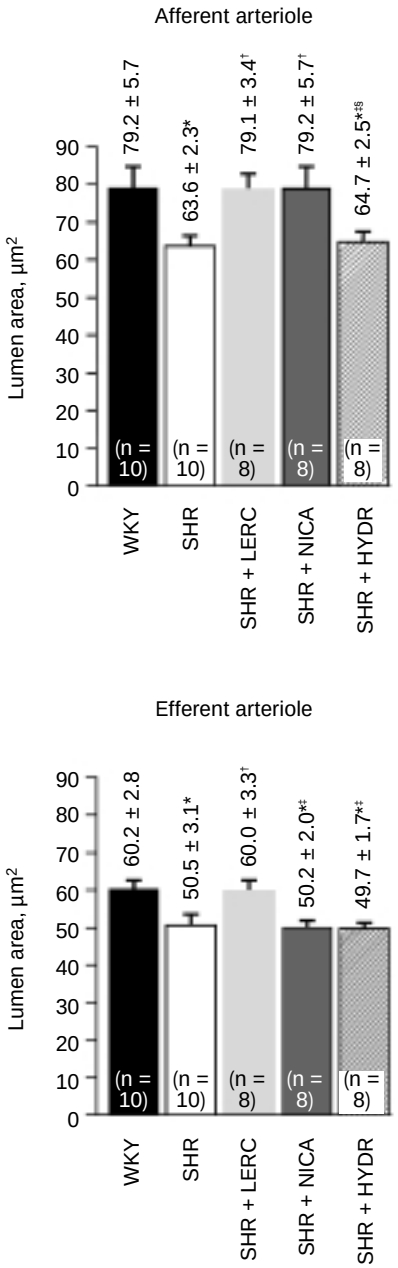

FIG. 2 Based on quantitative image analysis, lercanidipine countered hypertension-dependent changes in both afferent and efferent glomerular arterioles of different animal groups. Treatment with nicardipine dilated afferent but not efferent arterioles. Hydralazine had no effect on afferent or efferent arterioles. Values mean ± standard error. HYDR = hydralazine, LERC = lercanidipine, NICA = nicardipine, SHR = spontaneously hypertensive rats, WYK = Wistar-Kyoto rats. *$p < 0.05$ vs. WKY; †$p < 0.05$ vs. SHR; ‡$p < 0.05$ vs. SHR + LERC; §$p < 0.05$ vs. SHR + NICA. Source: Ref. No. 26.

ent and efferent arterioles may ultimately translate into renal benefits but, clearly, further clinical trials will be needed to determine these effects and the role that these agents may play in the management of hypertension among patient populations.

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