AJH 2002; 15:94S–97S

Calcium Antagonists in Hypertension: From Hemodynamics to Outcomes

Franz H. Messerli

Hypertension, by definition, is a hemodynamic disorder. A high cardiac output and a normal systemic vascular resistance characterize the young hypertensive patient. As hypertension progresses, resistance becomes progressively elevated and cardiac output returns to normal. The elderly patient with hypertension has very high systemic vascular resistance and low cardiac output. Antihypertensive drugs should not only lower arterial pressure but also bring other hemodynamic parameters as well as functional and structural changes of the cardiovascular system back to normal. With the notable exception of the classic β-blockers, all antihypertensive drug classes, including the vasodilating β-blockers, increase or maintain cardiac output and lower systemic vascular resistance. Calcium antagonists, although a very heterogeneous group, have been shown to have a similar effect on systemic hemodynamics. Initially, the short-acting agents (even verapamil) produce a reflex increase in heart rate and cardiac output with a decrease in systemic vascular resistance. This reflexive cardiac acceleration is not seen with the extended-release or longer-acting formulations, which usually maintain cardiac output and decrease systemic resistance. Lercanidipine is a novel calcium antagonist that has been shown to differ from other dihydropyridines in that the incidence of vasodilatory edema for any given decrease in blood pressure is less pronounced. Whereas all dihydropyridine calcium antagonists dilate the afferent arteriole in the kidney, preclinical studies have shown that lercanidipine also produces dilation of the efferent vessel. Similar balanced pre- and postcapillary vasodilation may be an explanation for the lower incidence of vasodilatory edema seen clinically with lercanidipine. These micro- and macrovascular features make lercanidipine an attractive new member in the arsenal of the powerful dihydropyridine calcium antagonists. Am J Hypertens 2002;15:94S–97S © 2002 American Journal of Hypertension, Ltd.

Key Words: Calcium antagonists, hypertension, dihydropyridines, lercanidipine.

Calcium antagonists are widely used antihypertensive agents and their use has increased dramatically during the past decade. Their wide appeal can be attributed to several features, including their well-documented antihypertensive efficacy, metabolic neutrality, and a clean side effect profile. If one accepts the surrogate end point of lowering blood pressure (BP) as the goal of antihypertensive therapy, calcium antagonists could be considered as ideal agents. They lower BP regardless of age, gender, race, salt intake, fluid volume status, concomitant drug therapy, and co-morbid conditions. With most drug classes used for the treatment of hypertension, until recently longitudinal studies documenting efficacy in preventing stroke, myocardial infarction, congestive heart failure or death were lacking. However, there are now three large prospective morbidity and mortality studies in which calcium antagonists were compared with placebo.[1–3] Furthermore, in three other major prospective studies, calcium antagonists were compared against other active therapy, such as diuretics and β-blockers, as well as angiotensin converting enzyme (ACE) inhibitors.[4–6] All six of these large multicenter studies attest to safety and efficacy of the long-acting calcium antagonists in the treatment of hypertension. Thus, within a very short period of time calcium antagonists have become, apart from diuretics, the drug class with best-documented safety and efficacy for reduction of morbidity and mortality in hypertension.

Classification Of Calcium Antagonists

Calcium antagonists are a very heterogenous drug class and differ not only in their molecular structure, sites, and modes of action on the L-type calcium channel, but also with regard to their effect on various other cardiovascular functions. For example, verapamil is less vasoselective, has a more negative inotropic effect, and elicits less activation of both the sympathetic nervous system and the renin angiotensin system than dihydropyridine calcium

Received March 28, 2002. Accepted March 28, 2002.

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0895-7061/02/$22.00
PII S0895-7061(02)02950-3

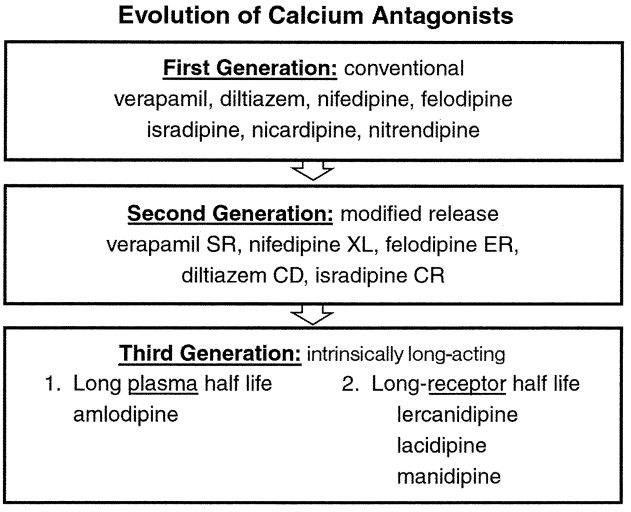

FIG. 1. Evolution of calcium antagonists. First generation agents require multiple dosing due to their short half-life. Second generation agents are once-a-day agents characterized by a delayed or modified release mechanism. Third generation agents are inherently long-acting agents. The long-receptor half-life agents characteristically have a great degree of lipophilicity.

antagonists. Verapamil, therefore, may be more appropriate for hypertensive patients with ischemic heart disease, particularly in the patient after a myocardial infarct.[7,8] Conversely, amlodipine, which has little negative inotropic effect and, at least in congestive heart failure, little neurohumoral stimulation, can safely be used in selected patients with congestive heart failure.[9] Moreover, it has become useful to classify calcium antagonists with regard to their duration of action into short-acting agents (to be given several times in a 24-h period) or into long-acting agents (to be given once a day). Short-acting agents should no longer be used for the treatment of hypertension because their powerful vasodilatory effect elicits sympathetic stimulation, possibly triggering angina, myocardial infarction, and stroke.[10,11] Long-acting drugs are commonly divided into three groups or generations (Fig. 1). Recent clinical studies have shown that it is not only the duration of action that is different among these three groups of long-acting calcium antagonists (discussed later).

Antihypertensive Efficacy

During the past decade, calcium antagonists have become the gold standard of antihypertensive efficacy. Among various dihydropyridine calcium antagonists, amlodipine is most often considered to be the prototype. This may not necessarily be due to its being more powerful in lowering BP than other dihydropyridine calcium antagonists, but perhaps more due to its extensive use by practicing physicians all over the world. In carefully selected populations, ACE inhibitors and angiotensin receptor blockers may be just as efficacious as calcium antagonists in lowering BP. However, in comparison to other drug classes, dihydropyridine calcium antagonists in a large spectrum of hypertensive patients including subjects who are on a high salt intake, African American, obese, taking nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors, or cyclosporin, in general exert marginally greater antihypertensive efficacy.

Effects on Morbidity and Mortality

Calcium antagonists have been tested against placebo and against other active therapy in several studies. A careful prospective meta-analysis of all studies in December 1999 showed equal morbidity and mortality reduction of calcium antagonist when compared to traditional therapy (β-blockers and diuretics) and ACE inhibitors.[12] Another very thorough recent meta-analysis has shown that calcium antagonists seem to be more efficacious in preventing strokes than conventional drugs, whereas ACE inhibitors seem to have an edge in preventing coronary artery disease and congestive heart failure.[13] In a recent study, the effect on renal function of an angiotensin receptor inhibitor was compared to a calcium antagonist in diabetic hypertensive patients.[14] The angiotensin receptor blocker had a clear advantage in reducing proteinuria and slowing down deterioration of renal function when compared to the calcium antagonist. Similarly, in the African American Study of Kidney Disease and Hypertension (AASK)[15] the amlodipine arm was discontinued because amlodipine provided significantly less nephroprotection than the other drug class. However, overall cardiovascular mortality and all-cause mortality was not different between the two treatment arms, neither in the Irbesartan Type 2 Diabetic Nephropathy Trial nor AASK.[14,15]

Adverse Effects

The most common adverse effects of long-acting dihydropyridine calcium antagonists is pedal edema.[16] Pedal or vasodilatory edema is clearly dose dependent and occurs in about 5% of patients on 5 mg of amlodipine, 25% of patients taking 10 mg of amlodipine, and in a much higher percentage in patients on 20 mg of amlodipine a day.[17,18] The edema seems to be related to arteriolar dilation, which increases intracapillary pressure and squeezes fluid volume from the intravascular space into the interstitium. Vasodilatory edema associated with dihydropyridine calcium antagonists responds well to agents that dilate the postcapillary vessel such as ACE inhibitors or angiotensin receptor inhibitor.[5,17,19] Among currently available long-acting dihydropyridine calcium antagonists there is very little difference in the incidence of vasodilatory edema. Thus, for a given decrease in arterial pressure, about the same incidence of vasodilatory edema can be expected with all presently available agents.

Lercanidipine

Lercanidipine is a new long-acting dihydropyridine calcium antagonist that has gained wide acceptance in Eu-

rope. In contrast to amlodipine, which is characterized by a long plasma half-life, lercanidipine has a relatively short plasma half-life but a long-lasting effect at the receptor and membrane level.[20] The vascular selectivity of lercanidipine is at least 10 times higher than that of amlodipine.[21] Also, it has a distinctly unique effect on the renal vasculature. Similar to nicardipine and amlodipine, lercanidipine dilates the afferent glomerular arteriole. However, in contrast to other dihydropyridine calcium antagonists, in preclinical studies lercanidipine has been shown to also dilate the efferent vessel.[22] This would mean that intracapillary pressure (and intraglomerular pressure, which leads to proteinuria) should be lower with lercanidipine than with other dihydropyridine calcium antagonists at the equipotent antihypertensive dose.

Twenty-four-hour ambulatory BP monitoring has shown that lercanidipine confers a smooth antihypertensive effect over a full 24-h period.[23] The antihypertensive efficacy of 20 mg of lercanidipine was not different from 10 mg of amlodipine on 24-h ambulatory BP monitoring. Of particular interest is the adverse effect profile of lercanidipine. Fogari et al[24] measured ankle–foot volume and pretibial subcutaneous tissue pressure in 60 hypertensive patients who were randomized to either lercanidipine or nifedipine gastrointestinal therapeutic system (GITS). The average increase in ankle–foot volume and pretibial subcutaneous tissue pressure was less than half with lercanidipine when compared to nifedipine GITS.[24] Finally, the tolerability of lercanidipine was compared to that of amlodipine and lacidipine in a double-blind, randomized, parallel group study by Leonetti et al[25] in more than 800 patients. Symptoms of heaviness and swelling in the lower extremities were distinctly more common in patients on amlodipine than in those on lercanidipine. More important, the incidence of edema was less than half in patients on lercanidipine than in those on amlodipine. Whereas in the lercanidipine group only 1.9% of patients dropped out because of edema, this percentage amounted to 8.0% in the amlodipine group. The investigators concluded that lipophilic dihydropyridines, such as lercanidipine and lacidipine, were significantly better tolerated than amlodipine when used as a single agent or in combination with other antihypertensive drugs.[25]

Conclusions

Efficacy and safety of calcium antagonists in hypertension has been established by no less than three large prospective morbidity and mortality studies against placebo and three equally large studies against active therapy, such as diuretics and β-blockers or ACE inhibitors. The wide appeal of calcium antagonists is the result of their well-documented antihypertensive efficacy, metabolic neutrality, and the clean side effect profile. The most common adverse effect seen with dihydropyridine calcium antagonists is vasodilatory pedal edema, which is dose dependent. Lercanidipine is a new lipophilic dihydropyridine calcium antagonist with a long receptor half-life that at a similar BP-lowering efficacy in double-blind studies was shown to have less pedal edema than amlodipine and nifedipine. Experimentally, lercanidipine has been shown, in contrast to other dihydropyridine calcium antagonists, to dilate not only the afferent but also the efferent glomerular arteriole. These features make lercanidipine an interesting new compound in the arsenal of antihypertensive drugs.

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