Hypertension Is Not All Alike Nor Are Its Treatments: Where Would a Better Calcium-Channel Blocker Fit in a Modern Treatment System?

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The dihydropyridine calcium-channel blockers (CCBs) are a most seductive class of antihypertensive drugs because of their great vasodilatory potency, which promptly can induce greater decreases in blood pressure (BP) than any other class. Thus, this drug class for many years has had far and away the highest annual multibillion-dollar sales in the industry, led by the prototype molecule, nifedipine, as Procardia XL, and later superseded by amlodipine. However, this broad practice has gradually revealed a serious side-effect profile, limiting their rational usage. Their adverse effects largely result from arteriolar over-dilation, which causes dose-related peripheral and, at times, possibly cerebral edema formation, plus sympathetic nervous system activation in response to induced hypotension. In turn, the reduced BPs are accompanied by increases in venous return (preload), leading to higher heart rates and cardiac outputs, and hence to more overperfusion with headache and a tendency for bleeding from the capillary dilation. These consequences demonstrate why these dihydropyridines can often worsen heart failure and why they are not usually indicated during an acute myocardial infarction or stroke, or even during nosebleeds, all of which occur more frequently in hypertensives.

To address these side-effect problems, the authors of this supplement have described the development of a new dihydropyridine molecule, lercanidipine, with a more attractive side-effect profile. It could potentially become more attractive as a natriuretic CCB for treating hypertension, possibly alone,

but better used in combination with an antirenin “R” drug (angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, or a beta blocker).^{1,2} Each of these three antirenin drug classes act to correct CCB-induced edema formation, and also to quiet its induced sympathetic nervous system overactivity, thereby correcting tachycardia and headache. In this way, lercanidipine could possibly replace diuretic therapy as the useful second hypotensive drug added to an antirenin system agent whenever this is necessary.^{1,2}

When antihypertensive drug therapy was introduced, most people believed that BP reduction per se, by whatever means, is the only goal of drug treatment. However, this strategy over the last 10 years or more, even when using the more potent new drugs, has continued to produce dismal treatment results, with correction rates of only 9 to 24% in various countries worldwide.¹

This means that the present treatment strategy is flawed and that we truly need to reexamine the popular belief that all hypertension is alike. Actually, we know that mechanistically there are two different types of hypertension: (1) salt-mediated, low-renin hypertension (identified by ambulatory plasma renin activity [PRA] < 0.65) involving some 30% to 35% of patients; and (2) plasma renin-mediated hypertension (identified by PRA > 0.65) occurring in the other 65 to 70% of patients.¹ Moreover, there are basically two types of antihypertensive drugs, the natriuretic antisodium-volume “V” drugs and the antirenin system “R” drug types as defined below.

Accordingly, the soul of all antihypertensive treatment is to get each patient on the correct primary and, when necessary, the correct follow-up drug types. Ambulatory plasma renin testing has recently become widely available, using a new robotic chemiluminescence direct renin (DR) test that, for the first time, matches the accuracy and sensitivity of the labor-intensive Sealey-Laragh Method. Thus, guided by an ambulatory plasma renin test, the sodium-volume mediated V patients (PRA < 0.65 or DR < 5.0) should be treated first with a natriuretic V drug (diuretics, spironolactone, a CCB, or an alpha blocker), while R patients (PRA > 0.65 or DR > 5.0) are first treated instead with one of the three antirenin R drug types (an angiotensin-converting enzyme inhibitor, angiotensin-recep-

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tor blocker, or a beta blocker), which will also protect these patients from later renin-angiotensin-mediated fatal heart attack, heart failure, stroke, or kidney failure. Follow-up renin testing also guides the correct second drug class choice for drug addition or subtraction in the uncorrected-treated patients.¹

Within the framework of this rational, biochemically and mechanistically targeted Laragh Treatment Method, it is quite possible that a new generation of improved CCB-natriuretic vasodilators, as exemplified by the lercanidipine profile, could have significant roles for implementing renin test-guided drug treatments. In this rational biochemical framework, the future of clinical science, and likely of lercanidipine usage as well,

for achieving better patient care to prevent renin-mediated fatal consequences and prolong useful lives is quite promising.

References

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