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Use of Aldosterone Antagonists in Resistant Hypertension

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Recent clinical trials indicate that resistant hypertension, defined as uncontrolled hypertension despite concomitant use of three or more antihypertensive agents, is common, affecting 20%-30% of the different study populations. Such clinical outcome studies provide our best estimates of the true frequency of resistant hypertension because they employed an intensive treatment regimen mandating drug titrations if blood pressure remained elevated, medications were provided at no charge, and adherence was closely monitored with pill counts. Given the size and diversity of the study population, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] may provide the best estimation of the prevalence of resistant hypertension. In ALLHAT, more than 33,000 subjects aged 55 years or older with a history of hypertension and one other cardiovascular risk factor were randomized to chlorthalidone, amlodipine, or lisinopril. The dose of the randomized medication was titrated first; nonstudy antihypertensive medications were then added as long as blood pressure remained above 140/90 mm Hg. After 5 years of follow-up, 34% of subjects had not achieved goal blood pressure and overall, 27% of subjects were receiving three or more medications.[1]

Other recent outcome studies document that resistant hypertension is not rare. In the Controlled ONset Verapamil INvestigation of Cardiovascular End Points trial (CONVINCE),[2] more than 16,600 subjects were randomized to controlled-onset, extended-release verapamil or conventional antihypertensive therapy (atenolol or hydrochlorothiazide), with other medications added as necessary to reduce blood pressure below 140/90 mm Hg. After a mean follow-up of 3 years, 33% of subjects had not achieved goal blood pressure and 17%-18% of subjects were receiving three or more antihypertensive medications. In studies of even more complicated patients with hypertension, control rates are even worse. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study,[3] which enrolled hypertensive patients with left ventricular hypertrophy, only 46%-49% of subjects had a blood pressure of <140/90 mm Hg after almost 5 years of intensive antihypertensive treatment.

Common factors associated with development of resistant hypertension include obesity, sleep apnea, diabetes, chronic kidney disease, older age, and high dietary salt ingestion. Interfering substances such as nonsteroidal anti-inflammatory drugs and excessive alcohol ingestion can worsen blood pressure control.

Hyperaldosteronism is being increasingly recognized as a common underlying cause of hypertension. In an extensive evaluation that included more than 600 subjects with hypertension, Mosso et al.[4] found that the prevalence of aldosteronism increases according to the severity of the hypertension. Applying Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure sixth report staging criteria to untreated subjects, primary aldosteronism was diagnosed in 2% of subjects with stage 1 hypertension (140-159 mm Hg/90-99 mm Hg), 8% of subjects with stage 2 hypertension (160-179 mm Hg/100-109 mm Hg), and 13% among subjects with stage 3 hypertension (>180/110 mm Hg). This is just one of many reports indicating a prevalence of hyperaldosteronism of 15%-30% among general and selected hypertensive populations.

Hyperaldosteronism is particularly common in subjects with resistant hypertension. In a prospective evaluation of African-American and white subjects with resistant hypertension, defined as uncontrolled hypertension despite use of three or more antihypertensive agents, we found an overall prevalence of aldosteronism of approximately 20%.[5] These results are consistent with a study from separate investigators reporting a prevalence of aldosteronism of 17% among subjects referred to hypertension specialists for uncontrolled hypertension.[6]

In our evaluation of the prevalence of hyperaldosteronism in subjects with resistant hypertension, we speculated that a frequency of true primary aldosteronism of 20% likely underestimated the contributory role of aldosterone excess in causing treatment resistance. Even in the absence of true primary aldosteronism, our evaluation indicated a large number of subjects with levels of 24-hour urinary aldosterone excretion that we believed were inappropriate given the associated low plasma-renin activity and high degree of dietary sodium ingestion. Based on that observation, we hypothesized that aldosterone blockade would be effective in a much larger proportion of these patients with resistant hypertension than just those with confirmed hyperaldosteronism.

To test this hypothesis, we assessed the blood pressure response at 1 month, 3 months, and 6 months of follow-up after adding low-dose spironolactone (12.5-50 mg) to the antihypertensive regimen of 76 subjects with resistant hypertension.[7] Before initiation of spironolactone therapy, renin-aldosterone status was characterized in terms of plasma-renin activity and 24-hour urinary aldosterone excretion. All subjects were on multidrug regimens that included a diuretic, an angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker. The mean dose spironolactone at the end of 6 months of follow-up was 30 mg daily.

Addition of low-dose spironolactone was associated with a mean decrease in blood pressure of 21±20 mm Hg/10±14 mm Hg at 6 weeks and 25±20 mm Hg/12±12 mm Hg at 6 months of follow-up (p<0.0001 compared with baseline for both the 6-weeks and 6-months time points). The reduction in blood pressure was similar in subjects with high urinary aldosterone excretion and subjects with normal or low aldosterone excretion. Also, the spironolactone lowered blood pressure equally in African-American and white subjects. Spironolactone was generally well tolerated. Approximately 10% of men complained of breast tenderness. Hyperkalemia (>5.5 mEq/L) occurred in two subjects, both with chronic kidney disease (creatinine clearance <50 mL/min). In five subjects, three of whom had diabetes, spironolactone use was associated with acute increases in serum creatinine levels in the setting of a substantial reduction in blood pressure. With down-titration of the spironolactone and stabilization of the blood pressure, renal function normalized in three of these subjects. In the two remaining subjects, renal function normalized with discontinuation of the spironolactone. This experience suggests the acute renal insufficiency in these subjects may have been secondary, at least in part, to the acute blood pressure reduction as opposed to a direct effect of spironolactone.

These results demonstrate that an aldosterone antagonist can be effective in treating hypertension resistant to multidrug regimens that include a diuretic and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Additional blood pressure reduction was also achieved in subjects without hyperaldosteronism. Benefit in such subjects may have been secondary to additional diuretic effects of the aldosterone antagonist or, as we hypothesize, reflects a broad role of aldosterone in causing resistant hypertension even in the absence of demonstrable hyperaldosteronism.

Recent clinical trials document the efficacy of eplerenone, a selective aldosterone antagonist, in treating hypertension in subjects with primary hypertension.[8-10] Based on our experience with spironolactone, we anticipate that eplerenone would likewise be effective as add-on therapy in subjects with resistant hypertension while avoiding the antiandrogenic and antiprogesteronic effects of spironolactone. Studies evaluating eplerenone specifically in this setting have not yet been done.

With an aging and increasingly obese population, the prevalence of resistant hypertension will undoubtedly increase. Even now, failure of multidrug regimens of three or more medications to control blood pressure is common. Our experience suggests that the use of aldosterone antagonists can provide significant blood pressure reduction in these difficult-to-treat patients. Such agents are generally safe and well tolerated. Hyperkalemia or acute renal insufficiency occur rarely, and should be monitored for, particularly in patients with chronic kidney disease and/or diabetes.

The general benefit of aldosterone blockade in subjects with resistant hypertension suggests that aldosterone excess may be a more common cause of hypertension than previously thought. However, the aldosteronism that we are reporting as being so common is undoubtedly different from the classic syndrome of primary aldosteronism first described by Jerome Conn.[11] The regulatory abnormalities, distinct from classic aldosteronism, resulting in such a high prevalence of aldosteronism are unknown. Elucidation of such abnormalities may allow prevention and/or development of even more effective treatment strategies.

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