Response to It Is the Plasma Renin Activity Level That Counts, not Stoichiometry

We have emphasized previously what Sealey and Laragh\(^1\) underline in their letter: plasma renin activity (PRA) directly measures the effect of renin inhibitors, whereas plasma renin concentration (PRC) only indirectly reflects a response to reduced PRA and angiotensin II levels. Direct measurement of PRC is subject to several shortcomings,\(^2,3\) which may be overcome by the addition of excess exogenous substrate.\(^4\)

Nevertheless, by counting the molecules of renin and its inhibitor (stoichiometry), a reasonable prediction of renin blockade can be made: despite a substantial rise in PRC at 24 hours after aliskiren intake, >95% of renin remains blocked, and neither PRA nor carefully measured angiotensin II concentrations are increased.\(^5\) Our initial and subsequent measurements of PRA and PRC in hypertensive patients treated with aliskiren tend to confirm the old Laragh hypothesis that “high-renin” subjects respond more markedly to renin inhibition than “low-renin” subjects, but there is no sign of any blood pressure–raising mechanism with this new class of drugs.\(^2,6\)

Sealey and Laragh\(^1\) refer to our article showing that aliskiren decreases PRA in a dose-related manner. A few PRAs were indeed above baseline after 4 weeks of treatment with aliskiren, mainly after the placebo-like 37.5-mg dose (Figure). Sealey and Laragh\(^1\) chose to redraw in percentages the PRAs that we had reported in absolute values. The Figure mentions our absolute values in the very low normal range (normal: 0.2 to 3.8 ng/mL per hour in seated subjects). Even in the placebo-like low-dose group of renin inhibition, the highest PRA obtained after an increase from baseline was well within the normal range, at 2.7

ng/mL per hour. No “dangerous” increase in PRA may be claimed from these data. Interestingly, among 161 patients treated with aliskiren, none of the 12 subjects with unchanged or increased PRA showed an increase of >10 mm Hg in systolic daytime blood pressure.

In contrast, among 197 hypertensive patients, there were 10 patients with blood pressure increases of >10 mm Hg (systolic daytime blood pressure) after 4 weeks of treatment (2 with losartan and 4 with 37.5 mg, 1 with 75 mg, 1 with 150 mg, and 2 with 300 mg of aliskiren). Although an increase in PRA after losartan treatment was no surprise, there was no increase measured in PRA of the 8 patients under aliskiren. Therefore, our data do not confirm that aliskiren could increase blood pressure by raising PRA. Stoichiometric considerations on PRC predicting efficient blockade of renin by aliskiren prevail.

Figure. Aliskiren reduces PRA in a dose-related manner. Normal units (U) of PRA: 0.2 to 3.8 ng/mL per hour. Data are from Stanton et al.\(^6\)

Disclosures


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1. Sealey JE, Laragh JH. It is the plasma renin activity level that counts, not stoichiometry. \(10.1161/HYPERTENSIONAHA.108.116483\)
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