Letter to the Editor

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The Renin Rise With Aliskiren: It's Simply Stoichiometry

To the Editor:

With great interest we read Campbell's[1] interpretation of plasma renin concentration in patients receiving aliskiren. The renin rise appears to be larger than the rise observed during angiotensin (Ang)-converting enzyme inhibition or Ang II receptor blockade.[2] Indeed, it has been suggested that this may lead to a rise in Ang II.[2] However, neither a rise in Ang II nor the putative subsequent rise in blood pressure have been observed thus far,[3] possibly because the apparent renin rise is attributable, at least partly, to an assay-related artifact, allowing prorenin to be detected as renin.[3,4]

Irrespective of the cause of this rise and whether the rise is exaggerated, an aspect that merits consideration is the renin-aliskiren stoichiometry. Is the number of aliskiren molecules in blood after aliskiren sufficient to block all renin molecules, even when renin has increased several-fold? Renin concentration measurements do not distinguish aliskiren-bound and free renin.

To address this question, we have made use of the measurements of renin (concentration and activity) and aliskiren plasma levels in 20 healthy subjects on a low-sodium diet receiving 3 escalating doses of aliskiren (75, 150, 300, or 600 mg).[5] Each subsequent aliskiren dose was given 2 days after the previous dose.

The Figure (top) shows that the aliskiren:renin ratio increases with each subsequent aliskiren dose up to 300 mg, reaching ratios of ≈20 000 after 5 hours and 1500 to 3000 after 24 hours. At higher doses, the ratio no longer increases, indicating that the rise in renin now matches the rise in aliskiren.

Two procedures were followed to estimate the percentage renin inhibition (Figure, bottom). First (closed circles), the measured and expected plasma renin activity were compared, the latter being calculated on the basis of the renin concentration reached during aliskiren treatment and the renin concentration-plasma renin activity relationship ($r=0.90$; $P<0.01$) without aliskiren. Second (open circles), inhibition was calculated on the basis of the aliskiren concentration, using the formula $100\times[\text{aliskiren}]/([\text{aliskiren}]+IC_{50})$, where IC_{50} represents the aliskiren concentration (0.6 nmol/L) that is required to inhibit 50% of the renin molecules. Both procedures yielded the same result, and correcting for the 50% of aliskiren that has been estimated to be protein-bound in plasma did not make a difference (data not shown).

The data show that renin inhibition is >99% at 5 hours after the 300- and 600-mg aliskiren doses and still >95% at 24 hours after these doses. Even at 48 hours, inhibition was >85% in both cases. The inhibition percentages reached after 150 mg of aliskiren were only marginally smaller. Obviously, when using aliskiren in the clinically available once-daily doses of 150 and 300 mg, the steady-state aliskiren levels will be even higher than the levels reached here. Clearly, therefore, the circulating aliskiren levels during regular aliskiren treatment are more than sufficient to obtain (near-) complete renin blockade, even at trough. The aliskiren-induced rise in renin is well below the 20- to 100-fold rise required to overcome 95% or 99% of renin inhibition. Thus, a rise in Ang II and/or blood pressure during prolonged aliskiren treatment is unlikely: it is the stoichiometry that counts and not the rise in renin!

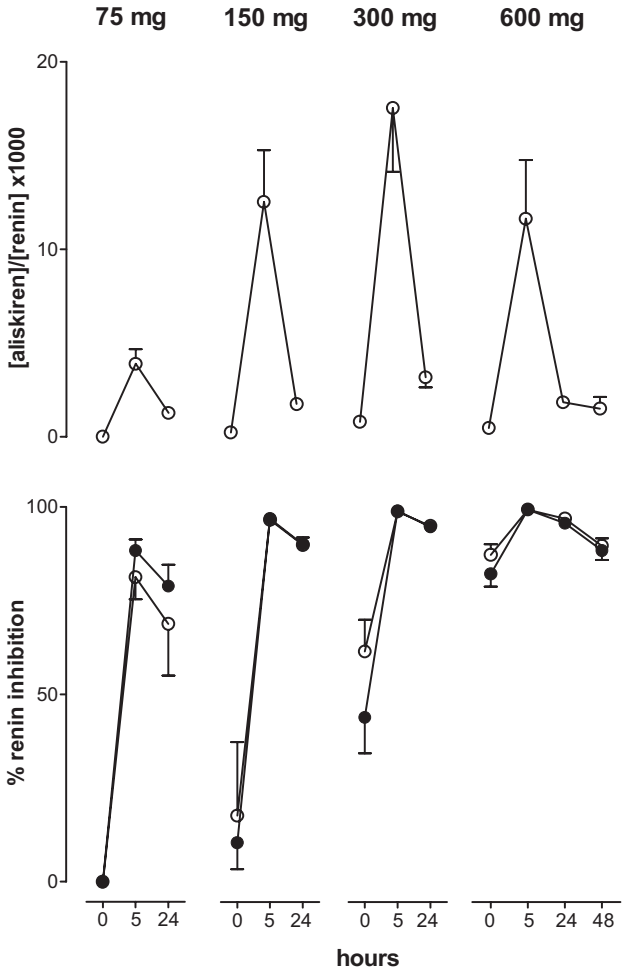

Figure. Top, Aliskiren:renin concentration ratio during exposure of 20 healthy subjects to escalating doses of aliskiren (75, 150, 300, or 600 mg) on separate study days. Each subsequent aliskiren dose was given 2 days after the previous dose, and t=0 of each dose after 75 mg corresponds with t=48 h after the previous dose. Bottom, Percentage of renin inhibition, calculated on the basis of the measured plasma renin activity and renin concentration (●) or the aliskiren concentration (○). See text for explanation.

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