Inhibition of renin secretion by angiotensin II receptor blockade?

To the Editor: The article in the June 2001 issue of Kidney International by Agarwal [1] suggests that in 16 patients with chronic renal failure during chronic angiotensin-converting enzyme (ACE) inhibition with 40 mg lisinopril/day, the addition of 50 mg losartan/day decreased plasma renin activity by 59%. This finding is unexpected since it has been well known from experimental animals that both ACE inhibition and angiotensin receptor blockade stimulate renin secretion and renal renin gene expression severalfold from baseline [2]. Furthermore, both 100 mg losartan and 80 mg quinalapril given for 10 days at this constant dose increased plasma renin activity 3- to 4-fold in 25 normotensive subjects on a controlled (low) sodium intake [3]. Finally, Stergiou et al recently demonstrated that the addition of 80 mg valsartan for 5 weeks to a maximal dose of chronic benazepril (20 mg for 6 weeks) significantly increased plasma renin activity in 20 patients with primary hypertension [4].

The above results of Agarwal [1] may be explained by several shortcomings of this study. First, baseline plasma renin activity before losartan treatment was 204% (!) of baseline plasma renin activity before placebo treatment, whereas plasma renin activities at the end of the respec-

tive treatments were very similar (i.e., 1.14 vs. 0.94 ng/mL/hour). Second, sodium intake was high and uncontrolled, allowing a lower baseline sodium excretion (=intake) before losartan treatment compared to placebo treatment (Δ sodium excretion 37 mEq/24 hours) and a higher sodium excretion at the end of losartan treatment (Δ sodium excretion 12 mEq/24 hours). Furthermore, the circumstances of blood sampling (i.e., supine position of patients for an unidentified period of time, fluid/food intake before taking blood samples) were not reported [1].

Therefore, the most plausible explanation for the plasma renin data obtained by Agarwal [1] may be methodological shortcomings and random fluctuations, but no real effect of losartan. Parenthetically, this could also hold true for the results of glomerular filtration rate (GFR) measurements, where GFR decreased (randomly) by 5 mL/min during placebo treatment (from 69 to 64 mL/min) and increased by 5 mL/min during losartan treatment (from 63 to 68 mL/min) [1].

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Reply from the author

I agree with Krämer et al that the increase in plasma renin activity (PRA) with add-on losartan therapy was unexpected [1]. However, I am unaware of any data in the population of patients that was studied to refute those findings. Brown, Agirbasli, and Vaughan compared angiotensin-converting enzyme (ACE) inhibitors with angiotensin II receptor blocker but did not study the combination in normotensive, sodium-restricted volunteers [2]. In the study by Stergiou et al, benazepril was used in a submaximal dose (20 mg/day) in patients with essential hypertension [3]. In contrast, our patients received lisinopril for an average of 18 months in a dose of 40 mg/day prior to participation in the trial. Such a dose is truly max-
imal, especially when considering the fact that elimination of lisinopril is predominantly renal and patients had impaired glomerular filtration rates (GFR) [4]. Furthermore, our patients with chronic renal failure were consuming a self-selected diet (one high in sodium), they were obese, and they had poorly controlled hypertension despite more than three medications. Therefore, this population, which is reflective of a large population of the chronic renal failure patients in the United States, is substantially different from those mentioned by Krämer et al.

Our baseline PRA levels appear different, however, because in the trial design (randomized two-period crossover) these PRA baselines, prior to losartan therapy, were obtained six weeks apart. We conducted analysis as suggested by Rosner for crossover trials and excluded carryover or sequence effects [5]. The statistical analysis of our data demonstrates that the likelihood of random chance accounting for our results of reduced PRA is <0.3%. Data on plasma aldosterone/PRA further support these findings. Similarly, urinary sodium excretion did not change statistically and is unlikely to account for our findings. The chance of random error causing GFR changes is 1.7%. As to the method of blood sampling for PRA, all samples were drawn in the morning after a half hour of supine rest in a quiet room.

Thus, I believe that our data are not due to methodologic flaws or randomness, but they were certainly unexpected. We do not have all the answers, but we speculate on the reasons that this may have occurred [1]. Furthermore, the primary end point of our trial was proteinuria, not perturbations in renin-angiotensin system or GFR. Thus, the results of our secondary outcomes should be considered exploratory, not definitive. We agree that our results do not fit the paradigm and that this needs further research.

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