Effects of Acute Angiotensin II Type 1 Receptor Antagonism and Angiotensin Converting Enzyme Inhibition on Plasma Fibrinolytic Parameters in Patients With Heart Failure

To the Editor:

We read with interest the study by Goodfield et al.1 comparing the effects of the acute administration of a single dose of enalapril or losartan on fibrinolytic parameters. We would like to raise several concerns about the design of this study that we believe should temper the authors' interpretation of their results. First, a well-described diurnal variation exists in plasminogen activator inhibitor-1 (PAI-1) antigen and activity. In this study, subjects received oral doses of enalapril and losartan at 10:00 AM; blood samples were drawn before drug administration and at 4:00 PM. However, in carefully controlled studies, we have shown that in subjects with an activated renin-angiotensin system (RAS), plasma PAI-1 antigen levels fall spontaneously by \( \approx 50\% \) over that same time period.2 Although the decrease in PAI-1 after losartan was greater than that measured after enalapril, it is possible that neither reduction was different from that which would have been measured during placebo. Second, the authors studied patients with congestive heart failure who were taking other medications that could affect the RAS. Without data on renin or aldosterone concentrations during each study day, it is impossible to exclude the possibility that the degree of stimulation of the RAS differed on the 2 study days. Third, because blood was sampled at only one time point after drug administration, the authors cannot exclude the possibility that they measured a pharmacokinetic rather than a pharmacodynamic effect. Finally, the relatively low affinity of enalapril for tissue angiotensin-converting enzyme may explain the apparent reduced potency of this drug in reducing PAI-1. However, the more likely explanation is that neither drug had any real effect on plasma fibrinolytic balance, with the reported results merely reflecting predicted diurnal changes and the effects of confounding variables.

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Response

We are grateful to Drs Vaughan and Brown for their comments and are pleased that they found our article of interest. They raise 4 relevant issues relating to our preliminary findings.

The diurnal variation of plasma tissue plasminogen activator and plasminogen activator inhibitor type 1 concentrations is important, well described, and considered in the discussion of our article. However, the comparison between enalapril and losartan is valid, and the crossover design enhances the power of such a comparison. Given the close proximity of the study days (48 hours) and the clinical stability of the patients enrolled, it is unlikely that there was a significant difference in the activation of the renin-angiotensin system between the losartan and enalapril phases of the study. A time order effect was not observed, and the order of enalapril and losartan was randomized. However, we are currently in the process of determining the baseline plasma renin activity, angiotensin II concentration, and aldosterone concentration on the 2 study days.

We do not believe that the observed differences between enalapril and losartan are due to a pharmacokinetic effect because, as we stated in the Methods section of our article, the 6-hour sampling time point was chosen to coincide with the peak plasma concentrations of the active metabolites, enalaprilat, and E3174. The interpretation that our findings reflect the relatively low affinity of enalapril for tissue angiotensin converting enzyme is an interesting hypothesis, and comparisons with more tissue-specific angiotensin-converting enzyme inhibitors, such as quinapril, would be of value.

Finally, in keeping with our submission as a Brief Rapid Communication, our article indicates “the need for further validation of the observations, elaboration of associated findings, and additional experimental trials.” Many issues remain unresolved, such as the effects of chronic dosing, the influence on diurnal variation, drug or class action, etc. However, we believe our preliminary findings suggest that, in patients with heart failure, a significant difference may exist in the effects of angiotensin-converting enzyme inhibitor therapy and angiotensin-I receptor antagonism on plasma fibrinolytic parameters.

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