LETTERS TO THE EDITOR

Long- Versus Short-Acting Angiotensin-Converting Enzyme Inhibitors

The article by Giles et al. (1) comparing the therapeutic effects of a long-acting angiotensin-converting enzyme (ACE) inhibitor, lisinopril, with a short-acting agent, captopril, in patients with heart failure is most timely as it addresses an issue of growing importance, that is, whether the various ACE inhibitors have any significant differences in therapeutic action. The increasing number of such agents being offered for clinical use urgently requires that such randomized comparative studies be undertaken.

Unfortunately, this article omits much vital information, precluding objective evaluation of its conclusions. First, captopril has a peak effect at 2 h, whereas lisinopril has a peak action at 6 to 8 h. Therefore, the timing of the exercise testing and the measurement of ejection fraction are critical to the evaluation, but no data as to the relationship of these assessments to dosing are provided in the paper. The primary end point, treadmill exercise testing, was not significantly different between the two drugs and was acknowledged as such. However, neither was the increase in ejection fraction when all the patient groups were analyzed (Fig. 4). It is only when the subgroup of patients with an ejection fraction ≤35% is tested that a significant difference emerges between the two drugs (Fig. 4). This figure is almost incomprehensible because the magnitude of difference in this subgroup is identical as for all patients: there are 18 patients fewer, yet the results are statistically significant for the subgroup but not for the total group. Whatever the statistics, one would like to know whether the subgroups in which significant differences were shown, ejection fraction ≤35%, for instance, were arrived at by retrospective subgroup analysis or had been prospectively defined for some reason. This is highly relevant to the reliance that can be put on the findings. There also does not appear to be any difference in the softer end points such as New York Heart Association class, Yale scales or cardiopulmonary ratio on the chest radiograph. Likewise, there is no significant difference in adverse effects.

Our impression of this report is that it is a negative study. It shows no important differences between the two drugs in the therapy of heart failure as defined by the authors. There are several methodologic defects that may have precluded a difference from being demonstrated.

It certainly provides no basis for the conclusions in the accompanying editorial by Jessup (2) that the study is "the first such comparison to show that clinical benefits occur more often with a specific ACE inhibitor." They may well do so, but the present study is inconclusive on this vital point. More pertinent is her final comment: "Unfortunately, until more research is accomplished, the choice of an ACE inhibitor for the patient with heart failure rests more on whimsy than on wisdom."

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References

Reply

Ikram and White fail to see the differences between the long-acting angiotensin-converting enzyme (ACE) inhibitor lisinopril and the short-acting ACE inhibitor captopril as found in our comparison trial of these drugs in patients with congestive heart failure. However, the differences in efficacy for a long-acting ACE inhibitor (lisinopril) versus a short-acting ACE inhibitor (captopril) in the treatment of patients with congestive heart failure are evident. The long-acting ACE inhibitor is given once daily, whereas the short-acting ACE inhibitor requires three times daily dosing. The peak effect of the two agents on blood pressure clearly occurs at different times: captopril 2 h after dosing, versus lisinopril 5 or 6 h after dosing (our Fig. 1). The slow onset of the long-acting ACE inhibitor accompanied by prolonged and even suppression of the adverse cardiovascular effects of unsustained suppression of the activated renin-angiotensin-aldosterone system in patients with congestive heart failure, may also be an advantage. On the other hand, the unsustained suppression of the renin-angiotensin-aldosterone by the short-acting ACE inhibitor captopril may produce a roller-coaster effect of activation and inhibition with resultant hemodynamic consequences. Because of restrictions on scheduling patients for ejection fraction and exercise tests, these tests were done within 2 to 3 h of the dose, which may have favored the short-acting ACE inhibitor peak effects. However, the peak changes in blood pressure may not be as important as ACE inhibition in tissue systems (1) for predicting long-term changes in exercise duration or ejection fractions.

The primary end point, treadmill exercise duration, was improved from baseline for the short-acting and long-acting ACE inhibitors. However, exercise duration with the long-acting ACE inhibitor was numerically greater than that with the short-acting agent. This numerical difference was statistically significant (p ≤ 0.05) when protocol violators were excluded from the analysis. Two subgroups of patients, the elderly group and patients with renal impairment, had significantly improved exercise duration with the long-acting ACE inhibitor.

For the all-patients-treated analysis, the increase in ejection fraction with the long-acting ACE inhibitor was significantly (p < 0.001) increased from baseline, whereas the short-acting ACE inhibitor failed to show this improvement (p = 0.2271). The difference between the short-acting and long-acting agents' effects on...