Fasidotril: The First Dual Inhibitor of Neprilysin and ACE

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ABSTRACT

Fasidotril represents the first member (13) of a new class of drugs which combines the effects of both ACE and NEP inhibitors in the same molecule, displaying a unique cardiovascular profile in hypertension and heart failure. In experimental hypertension, fasidotril exhibited a large profile of activity, being effective in both renin-dependent and volume-dependent models, which suggests its utility as monotherapy in a broad range of patient types. In patients with mild-to-moderate essential hypertension, fasidotril treatment produced a sustained decrease in systolic and diastolic pressures with a progressive effect, indicating that slowly occurring mechanisms, in addition to those of pure ACE inhibitors, were implicated in the antihypertensive activity.

In experimental heart failure, comparison of fasidotril to captopril in a rat model of myocardial infarction showed some advantages for the dual inhibitor. Firstly, fasidotril was found to be more effective than captopril in reducing cardiac hypertrophy at doses equipotent to those required to inhibit circulating ACE. Secondly, fasidotril, like pure ACE inhibitors (36,49,54), improved the survival of rats with myocardial infarction. However, contrary to ACE inhibitors, it did not lower blood pressure of infarcted rats. This lack of hypotensive effect is of interest since it maintains tissue perfusion, especially at the renal level, and is favorable to the full expression of the renal effects of ANP that are very sensitive to the renal perfusion pressure (27). The blunted renal responses to ANP that have been reported in severe congestive heart failure (8,18) are probably partly mediated by an excessively low blood pressure. One of the challenges of treating patients with heart failure is to balance systemic vasodilation and a potential consequent reduction of glomerular filtration. In this respect, fasidotril could represent an attractive candidate for use in the acute and subacute phases of myocardial infarction.

Although the mechanisms of action of dual ACE/NEP inhibitors are probably complex and deserve further studies, interference with various neurohumoral systems appears to be an attractive new approach to the therapy of hypertension and heart failure. Further trials will determine the clinical value of fasidotril in these pathologies.
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