Use of ‘Xapril’ in Patients With Chronic Heart Failure
A Paradigm or Epitaph for Our Times?

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One of the byproducts of the current rush to cost containment and health care reform has been a tendency for hospital and government formularies to limit the choice of drugs in a particular class. Often only one drug in a given class may be chosen for use, and increasingly, that choice is based on cost rather than patient benefit.

Recently several hospital and government pharmacies have chosen “Xapril” as the only angiotensin-converting enzyme (ACE) inhibitor that will be available on their formulary. Xapril has been approved for use by the Food and Drug Administration for use in hypertension but is not as yet approved for use in heart failure. Limiting the choice of the physician to one ACE inhibitor forces the physician who relies on the formulary to use Xapril for patients with heart failure as well as for hypertension. While Xapril was likely chosen because it was the cheapest ACE inhibitor available to the formulary, one must wonder whether it is the best choice for our patients or in the long run the cheapest for our health care system. To date, only enalapril has been shown to be effective in reducing mortality in patients with chronic heart failure. In the Consensus, SOLVD Treatment, and V-HeFT II trials, enalapril in a dosing strategy beginning with a test dose of 2.5 mg BID and up, titrating, if tolerated, to a dose of 10 mg BID, was shown to be effective in reducing mortality and the incidence of recurrent heart failure. Captopril has been shown to be effective in reducing mortality and is approved for use in the postinfarct patient with a left ventricular ejection fraction of ≤40%. In the SAVE study, the dosing strategy of captopril began with a test dose of 6.25 mg TID, which was titrated up to 50 mg TID if tolerated. Captopril has also been approved for use in chronic heart failure to improve exercise tolerance and symptoms. There also have been recent data suggesting that ramipril in a dose of 5 mg BID is effective in reducing mortality in postinfarct patients with clinical evidence of heart failure. There are no data on the effectiveness of enalapril or captopril in reducing mortality using dosing strategies other than those described in the major trials. The only other ACE inhibitors currently approved for use in heart failure are lisinopril and quinapril. Lisinopril and quinapril have been approved on the basis of an improvement in exercise tolerance and symptoms in patients with chronic heart failure. While it appears likely that the effect of ACE inhibitors in reducing mortality in chronic heart failure is a class effect, there is less certainty as to the dose of a given ACE inhibitor that will be effective in reducing mortality. There are clear differences between ACE inhibitors in lipophilicity, tissue binding, duration of action, metabolism, and excretion, all of which may potentially be of importance both for dosing and effectiveness.

The recent experience with flosequinan in the Praise Trial has emphasized the risk in using exercise performance and symptomatic improvement as a surrogate for mortality in patients with heart failure. Flosequinan has been shown to be effective at a dose of 100 mg orally in improving exercise tolerance and symptoms in patients with chronic heart failure maintained on conventional therapy including diuretics, digoxin, and an ACE inhibitor. On the basis of these data, flosequinan was approved for use in chronic heart failure in March of 1993. In June of 1993, it was found that flosequinan in a dose of 100 mg daily significantly increased mortality, and it was subsequently withdrawn from further marketing in the United States. The importance of dose has been emphasized recently by the experience with vesaninone. At a dose of 60 mg QD, vesaninone appears to improve survival, whereas at a dose of 120 mg QD, it decreases survival.

It would indeed be unfortunate if the dose of Xapril chosen for use in chronic heart failure on the basis of experience in the therapy of hypertension and small trials of exercise performance in heart failure proved to be ineffective in reducing mortality and morbidity. The clinician might have some reservation using agents such as lisinopril or quinapril, which, although approved for use in chronic heart failure, have not as yet been shown to reduce mortality in this situation. The clinician should, however, have great concern using Xapril, an agent not shown to be effective in reducing exercise performance, morbidity, or mortality in heart failure when other ACE inhibitors that have clearly been shown to be effective are available. The effective dose of a drug for an indication such as heart failure may not be the same as for hypertension. Often, the dosage used for the therapy of hypertension with an agent such as

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*Xapril is a pseudonym for an ACE inhibitor currently approved by the Food and Drug Administration for use in hypertension but not in chronic heart failure. A pseudonym was chosen rather than the name of the drug to focus attention on the general problem rather than the specific drug.
captopril is lower than that found to be effective in reducing morbidity and mortality in patients with systolic left ventricular dysfunction. There are as yet no prospective trials that are available that have compared relatively low doses of an ACE inhibitor, which may be effective in reducing blood pressure such as 12.5 to 25 mg BID to TID of captopril, with high doses such as captopril 50 mg TID, which have been shown to be effective in reducing mortality in patients with left ventricular dysfunction. The clinician, and more importantly, the patient, takes a risk in using a drug such as Xapril in chronic heart failure when there are little data showing its effectiveness in this situation.

As we search, as we should, for more cost-effective therapies and strategies, we should not abandon our responsibility in providing our patients the best care for the short-term benefit of saving a few dollars. We should strive to reduce cost but simultaneously demand that the decisions for the selection of a given therapy or strategy be made on the basis of a critical review of the data rather than providing financial gain to ourselves, our hospital, or health care system, lest the use of Xapril in heart failure prove to be not a paradigm but an epitaph for our times.

References

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