ST. MICHAEL'S HOSPITAL
Cardiology
UNIVERSITY OF TORONTO

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Felodipine as adjunctive therapy in failing hearts improves left ventricular emptying.

Reported and discussed by: Stuart Hutchison, MD

Introduction

The Veterans Administration has made numerous landmark contributions to the treatment of coronary artery disease and to the treatment of chronic congestive heart failure. The Veterans Cooperative trial[1] on coronary bypass surgery was one of the three pillar trials defining the contributions of CABG. The V-HeFT I study[2] documented that vasodilator therapy with isosorbide dinitrate/hydralazine improved survival in patients with NYHA class 2 or 3 heart failure, and the V-HeFT II study[3] determined that enalapril was superior to isosorbide dinitrate/hydralazine as a vasodilator in this setting. At the recent American Heart Association meetings in New Orleans, Dr. Jay Cohn et al presented a paper on the echocardiographic substudy of V-HeFT III.

V-HeFT III: Echocardiographic substudy

V-HeFT III is a randomized double blinded, placebo controlled study of the use of felodipine as adjunctive therapy in CHF. Felodipine is a second generation calcium channel blocker, without myocardial depressant effects. V-HeFT III comprised 450 males with class 2-3 NYHA heart failure on diuretic and ACE-inhibitor. The primary end-points of symptoms, quality of life and exercise tolerance were not affected by felodipine. Doppler echocardiograms were analyzed in 114 felodipine and 131 placebo patients at baseline and at 12 months. Table I demonstrates significant improvement in hemodynamics and echocardiographic measurements with felodipine by comparison to placebo.

The authors concluded that felodipine, when added to standard therapy for 1 year in patients with heart failure, reduced blood pressure and increased ejection

St. Michael's Hospital
30 Bond St., Suite 701A
Toronto, Ontario M5B 1W8
Fax: (416) 864-5330

TABLE 1

Variable	Felodipine	Placebo	P
BP systolic (mm Hg)	120±17 -7±15	123±16 +4±19	<0.01
BP diastolic (mm Hg)	73±11 -4±9	74±8 +2±10	0.01
Ejection fraction	0.29±0.09 +0.04±0.09	0.29±0.09 +0.01±0.09	0.01
Stroke index (ml/m^2)	24.7±8.1 +3.9±11.5	25.1±7.4 +1.0±9.3	0.03
LV end diastolic diameter (cm)	6.46±1.08 -0.09±0.83	6.51±0.85 -0.06±0.55	NS
LV end diastolic diameter/length	0.77±0.14 -0.01±0.14	0.78±0.10 +0.00±0.09	NS

fraction and stroke index, without affecting the size or shape of the left ventricle. The hemodynamic benefit did not appear associated with clinical benefit.

Hemodynamic benefit vs clinical improvement

How can the lack of clinical benefit, on the background of improved hemodynamic benefit be explained? It is possible that the duration of the trial was inadequate to observe a significant clinical benefit. In patients with severe heart failure (NYHA class 4) survival benefit can be demonstrated in a half year (CONSENSUS -1[4]), but in patients with class 2 or 3 heart failure, demonstration of survival benefit from vasodilators generally takes two or more years to observe (SOLVD trial: 3.5 years,[5] V-HeFT I: 2.3 years mean[2] V-HeFT II 2 years mean[3]). ACE-inhibitor use was standard in this trial. Is it, therefore, possible to improve on the benefits of ACE-inhibitors with the use of adjunctive vasodilators? In other words, most of the potential benefit may have been already realized by the use of the ACE-inhibitor. As such, failure of felodipine to contribute clinical benefit as an ancillary vasodilator does not mean that it may not do so as a first choice vasodilator. A possible sequel to this trial, as no detriment was seen with felodipine, and some suggestion of hemodynamic benefit was sustained, would be that felodipine be tested as a vasodilator agent of first use.

Safety of felodipine

It is noteworthy that the use of a calcium channel blocker was not associated with an increased adverse outcome. There has been such vociferous, often strident, debate on the topic of use of calcium channel blockers, that along the way, there have been many casualties, more than just trees in Oregon. It has become difficult to remember where prospective randomized blinded trials have demonstrated harm or help from calcium channel

blockers. In chronic congestive heart failure the short acting form of nifedipine worsens hemodynamics, and causes increased need for diuretics and hospitalization.[6] Post non-Q wave infarction, diltiazam increases late congestive heart failure in patients with reduced left ventricular ejection fraction.[7] At the 1 year point in this trial, neither adverse nor beneficial clinical outcome was demonstrated. These observations are commensurate with those of the PRAISE trial that failed to demonstrate a significant reduction in mortality (p=0.07) in chronic congestive heart failure patients treated with amlodipine.[8] Protagonists would cite the lack of adversity, antagonists would cite the lack of benefit. Certainly safety of amlodipine and felodipine in heart failure patients appears acceptable.

What to make of the hemodynamic benefit from felodipine? Evidently, felodipine is a vasodilator which produces demonstrable effects even on the background of another vasodilator. If favorably altering hemodynamics may lead to clinical benefit and improved survival, then it would seem to be a reasonable possibility that felodipine is laying the foundation for such a clinical benefit. Mortality benefits are hard won in congestive heart failure, and usually take years to achieve. But, if favorable hemodynamic alterations lead to improved exercise tolerance, and later to improved mortality, then wouldn't one expect improved exercise tolerance within a year of starting the drug? Why wasn't it seen here within a year?

Stroke volume data were offered, but not cardiac output. If felodipine resulted in a small suppression of sinoatrial node automaticity, then the cardiac output (stroke volume x heart rate) would fail to increase despite an improvement in stroke volume.

Should surrogate endpoints such as hemodynamic measurements be used? How helpful are they? Preliminary data presentation such as this raise these questions. Clearly, primary clinical endpoints (mortality and morbidity) are what we are most interested in. Assessment of clinical endpoints requires large patient numbers, therefore, lack of clinical benefit may reflect insufficient power. Whether hemodynamic benefit can be used as an indicator of clinical benefit (if larger sample size was used) remains uncertain and controversial. Clinical and hemodynamic benefit in this study does not match, but it is not in the opposite direction, and therefore, not truly conflicting.

Summary and Conclusions

These results suggest that the use of calcium channel blockers in CHF is not as proven as the use of ACE-inhibitors. ACE-inhibitors have many effects, both hemodynamic and tissue effects. They are more than just vasodilators, and appear to have many tissue effects that would appear desirable, but whose relevance is far from understood. It has been suggested that calcium channel blockers have tissue effects and may be anti-atherogenic,[9] however, much more work is required to elucidate these effects. In the meantime the use of Ca-antagonists in CHF is of unproven value.

Felodipine appears safe, as was seen with amlodipine in the PRAISE trial, but as an adjunctive vasodilator, its role remains to be proven.

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