SOUTHWESTERN NEWS

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BETA-BLOCKER SHOWN TO BE INEFFECTIVE IN PATIENTS WITH ADVANCED HEART FAILURE

DALLAS – May 31, 2001– A promising beta-blocker did not prolong survival of patients with advanced heart failure, according to a study conducted by researchers at UT Southwestern Medical Center at Dallas.

Bucindolol, an investigational medicine that is not approved by the Food and Drug Administration but in preliminary trials has been shown to be safe, effective and well-tolerated, did not reduce death from moderate-to-severe heart failure in 2,708 patients who took part in the Beta-Blocker Evaluation of Survival Trial (BEST). Patients with less-advanced heart failure did, however, show improvement with bucindolol. The National Heart, Lung and Blood Institute and the Department of Veterans Affairs sponsored the trial.

The results of the study are published in today's *New England Journal of Medicine*.

"We felt that this would be a great drug to use in heart failure. All of the preliminary studies in heart failure showed that it was well-tolerated and patients did great on it," said Dr. Eric Eichhorn, professor of internal medicine at UT Southwestern, director of the cardiac catheterization laboratory at the Dallas Veterans Affairs Medical Center and co-author of the study. "Although the primary result in the BEST study is that bucindolol reduced all causes of mortality by 10 percent, it was not a significant reduction."

The researchers found that nonblacks had a nominally significant reduction in mortality while taking bucindolol, while black patients did not.

The black patients enrolled in the study were younger and had more hypertension, diabetes and renal insufficiency and were slightly sicker than nonblacks in the study, Eichhorn said. "Although these results may represent a chance finding, the reason for the lack of beneficial response in this population is not entirely clear. We don't know if it's related to genetics or because the black patients were sicker. We're looking at the data now to determine that."

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Beta-blockers – which are used to prevent second heart attacks and to treat angina, hypertension, arrhythmia and migraine headaches – work by inhibiting the receptors of the stress hormone norepinephrine, which is involved in the progression of heart failure. Norepinephrine is activated by the adrenergic nervous system and stimulates the heart to beat faster.

Bucindolol is the only beta-blocker that has been tested in humans that blocks the beta 2 receptor and prevents norepinephrine from being released. Bucindolol's ability to inhibit the release of this hormone and block its receptors may not be well-tolerated in patients with advanced heart failure because of the rate at which the levels of the hormone are dropped.

"The failing heart relies on adrenergic support for contracting, but over time high levels of norepinephrine are harmful to the heart muscle," said Lucille Marcoux, clinical research coordinator of the study at the Dallas VA.

"We know that if we block some of the receptors, we can attenuate the progression of heart failure. Patients who have very advanced heart failure may have a difficult time compensating or adjusting for that withdrawal, so they don't tolerate the medicine as well," she said.

Levels of the hormone dropped nearly twice as much in black patients as nonblacks, which may account for the high incidence of mortality in these patients, Eichhorn said.

Bucindolol did, however, significantly reduce the incidence of hospitalization due to illnesses related to heart failure in all patients. A reduction in deaths from cardiovascular disease and a reduction in the combination of death and the need for heart transplants were also found in all patients taking bucindolol. There was no variation in the drug's effects based on gender.

"There is no doubt that beta-blockers play a key role in the treatment of mild to moderate heart failure," said Dr. Claude Lenfant, director of the NHLBI. "But its use for more severe heart failure, particularly with black patients, is now questionable."

Eichhorn added, "I think the take-home message for the study is that we need to make sure that traditionally underrepresented groups – females, African-Americans, Asians and Hispanics – respond in a similar fashion to our therapies. The study has raised the questions of possible genetic differences that may be present that we need to examine."

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Seventy percent of the participants in the BEST study were white; 23 percent were black; and 7 percent were Asian or Hispanic. At the time of enrollment, 92 percent of the participants had moderately severe heart failure (Class III), and 8 percent had severe heart failure (Class IV), as designated by the New York Heart Association. Half of the patients were administered bucindolol, and half received a placebo. The study was conducted at 90 clinical sites in the United States and Canada.

The trial, which was originally scheduled to end in June 2000, was stopped in July 1999 at the recommendation of the data and safety monitoring board because there was no significant difference in mortality in the two groups. A total of 449 deaths had occurred in the placebo group and 411 deaths in the bucindolol group.

Earlier this month, two other UT Southwestern research groups published their findings on two different drugs used to treat heart failure – a beta-blocker and an ACE inhibitor – in *The New England Journal of Medicine*. The results of the U.S. Carvedilol Heart Failure Trials Program found that the beta-blocker carvedilol reduced the risk of death and the symptoms of mild-to-moderate heart failure in black patients as well as it did in nonblack patients. Another study found that the ACE inhibitor enalapril maleate was less-effective in treating heart failure in black patients than in white patients.

Dr. Paul Grayburn, professor of internal medicine and chief of cardiology at the Dallas VA, also participated in the BEST study, which was funded by the NHLBI, the Department of Veterans Affairs and Incara Pharmaceuticals.

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