Oral Inotrope Shown Safe, but Not Effective

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STOCKHOLM — An oral inotropic drug was safe but not effective in a pair of studies that together enrolled more than 1,800 patients with advanced heart failure.

Although the Studies of Oral Enoximone Therapy in Advanced Heart Failure (ESSENTIAL) failed to show that enoximone could cut the incidence of death or cardiovascular hospitalization, the fact that the drug was safe means that it is eligible for further testing in very sick heart failure patients, Michael Bristow, M.D., said in an interview at the annual congress of the European Society of Cardiology.

"We have a lack of effective medications for very sick patients with decompensated heart failure," especially those with recurrent episodes of acute decompensation, said Dr. Bristow, codirector of the Cardiovascular Institute at the University of Colorado in Denver. "Enoximone has now been [proved] safe, and we saw a signal of efficacy in the sickest patients."

The studies enrolled 1,854 patients with New York Heart Association class III or IV heart failure at 211 centers in 16 countries. One study was done in North and South America; the other was done in Europe.

The patients also had a left ventricular ejection fraction (LVEF) of 30% or less and had had at least one hospitalization or two outpatient visits for worsening heart failure during the year before they entered the study. All were already on optimal treatment with both a β-blocker and an ACE inhibitor or an angiotensin-receptor blocker.

The patients were randomized either to placebo or to 25 mg enoximone t.i.d. After 2 weeks, the dosage was raised to 50 mg t.i.d for patients who weighed more than 50 kg and had no adverse effects from the lower dosage. These dosages were substantially lower than were those in previous enoximone studies.

After an average follow-up of 16.4 months, there was no significant difference between the two arms in either all-cause death, the major safety end point, or in all-cause death and cardiovascular hospitalizations, the major efficacy end point, said Marco Metra, M.D., professor of cardiology at the University of Brescia (Italy).

In the American but not the European study, treatment with enoximone was linked with a significant increase in a secondary end point measured by a 6-minute walk test done after 6 months of treatment. The two treatment arms showed no significant difference for the third efficacy end point of the study, patients' self-assessment of symptomatic improvement.

In a prespecified subgroup analysis that assessed efficacy responses in patients with an LVEF below the median for all patients (25%) and in those with an ejection fraction above the median, treatment with enoximone in patients with the worst left ventricular function was associated with a 10% reduction in both all-cause death and in deaths and cardiovascular hospitalizations, compared with placebo.

Enoximone treatment in the subgroup was also linked with a mean gain of 15 m in a 6-minute walk distance, compared with the placebo group. Further analyses of results in the sicker patients also showed enoximone treatment was especially effective for reducing deaths and hospitalizations after the first 16 months of treatment.

Enoximone is in the same inotropic class as milrinone. But enoximone is a pure phosphodiesterase inhibitor, which, along with its use in the setting of β-blocker treatment, may lead to its increased safety, said Dr. Bristow, who is also chief science and medical officer for Myogen, which sponsored ESSENTIAL and markets an intravenous formulation of enoximone (Perfan) in Europe, in an interview. ■

PRO & CON

Is nesiritide safe and effective for acute decompensated heart failure?

YES

Nesiritide is identical to endogenous B-type natriuretic peptide. How could a naturally occurring peptide that promotes vasodilation, facilitates natriuresis, and reduces neurohormonal activation be unsafe?

As clinicians, we do have to answer whether nesiritide is safe, effective, and appropriate for clinical care of patients with acute decompensated heart failure. We should stay within the Food and Drug Administration indications, and use nesiritide (Natrecor, Scios Inc.) only for patients with acutely decompensated heart failure who have dyspnea at rest or with minimal activity.

Some suggest that nesiritide causes an adverse rise in serum creatinine and increased risk of mortality. The doses used in studies citing dangerously elevated creatinine levels were 50%-600% higher than standard doses. At the doses we currently use, serum creatinine levels do not increase in a statistically significant way.

Three trials are often cited by those proposing an increased risk of mortality with nesiritide: the Nesiritide Study Group Efficacy Trial (NSGET); the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial; and the Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients With Natrecor (PROACTION).

However, these studies were not designed to assess mortality. In addition, when data are combined in a selective metaanalysis, the *P* value only demonstrates a trend toward increased mortality, not a statistically significant association (JAMA 2005;293:1900-5).

If, as Jonathan Sackner-Bernstein, M.D., and his colleagues suggest in the JAMA study, a single infusion of nesiritide in acute settings increases risk of mortality by 74%, then we should see similar risk in long-term, outpatient use. But we do not see this in the Follow Up Serial Infusions of Nesiritide Trial (FUSION I) (Am. J. Cardiol. 2004;94:595-601).

Findings of the Acute Decompensated Heart Failure National Registry (ADHERE) study also suggest an increased risk of death with nesiritide (Rev. Cardiovasc. Med. 2003;4:S21-S30). However, this was a very heterogeneous group. There was a greater than 1,000 times variation in risk of death in the ADHERE registry. In addition, in-hospital mortality actually decreased in those treated with nesiritide.

So, does nesiritide increase the mortality risk in acute decompensated heart failure? The answer is no, based on all currently available data.

Is the drug effective? The VMAC trial is the only double-blind, randomized study that demonstrates its efficacy (JAMA 2002;287:1531-40). There were 489 participants in VMAC, a phase III, placebo-controlled study conducted at 55 U.S. centers. Nesiritide was given in addition to standard therapy.

The prespecified primary objectives—improvements in 3-hour pulmonary capillary wedge pressure and patient-reported, 3-hour symptom relief (dyspnea)—were achieved with nesiritide, compared with standard therapy. Therefore, nesiritide is effective in patients with acute decompensated heart failure, based on the results of a randomized, controlled clinical trial. ■

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NO

Physicians consider that a drug should be withdrawn from the market if and when it is proven to increase the risk of death or major morbidity.

However, federal regulations set a different standard. If a drug is not shown to be safe, based on the evidence available at the time of approval in combination with evidence obtained subsequently, in the population for which it is intended, it shall be withdrawn.

To date, the results from controlled clinical trials have not shown nesiritide to be safe and fail to show that nesiritide provides clinically relevant benefit. Therefore, according to the Food, Drug, and Cosmetic Act, nesiritide should be withdrawn from the market.

Two recent metaanalyses brought to light important findings regarding the safety of nesiritide. First, a metaanalysis of all the trials showed a statistically significant 40-50% increased likelihood of worsening renal function associated with its use (Circulation 2005:111;1487-91). The increase was 40%-50% more likely with nesiritide, with every dose of nesiritide studied associated with a higher likelihood of renal risk, either significantly or showing a trend.

The second metaanalysis asked whether nesiritide was associated with a risk of death (JAMA 2005;293:1900-5). Coincident with federal regulations, this metaanalysis focused on the safety of the drug in the intended population, those with acutely decompensated heart failure as assessed in three studies. This analysis estimated that nesiritide was associated with an 80% increased risk of death within 30 days of administration. The revised product label includes a metaanalysis, which included even those studies that enrolled patients without acute heart failure, and estimates a 35% higher risk of death.

Many have argued that these analyses published in Circulation and JAMA do not prove that nesiritide is dangerous. The crucial observation is that no analysis shows that the drug is safe, and therefore, it must be withdrawn.

It is true that Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) was a positive trial. However, the relevance of change in wedge pressure is dubious for a drug that is not shown to be safe, unless there is a clinically meaningful benefit.

In VMAC, the only parameter that was significantly different from placebo was the dyspnea score after 3 hours. When asked at the same time how they felt overall, nesiritide and placebo treated patients did not respond differently. This was the same for the effect of nesiritide on the secondary end point of dyspnea score after 1 hour, and in fact, there was no time before the end of the third hour when there were any differences between nesiritide and placebo on patient perceived dyspnea or global well being.

With no meaningful difference in how patients felt, no difference on hospital length of stay or readmission rate, and the likelihood that the drug is dangerous, it's terribly difficult to understand why nesiritide would be used clinically.

Nesiritide now represents an interesting study of pathophysiology, drug marketing and regulatory error. As dictated by the Food, Drug and Cosmetic Act, the FDA must withdraw nesiritide. ■

Jonathan Sackner-Bernstein, M.D., is a cardiologist who practices in New York. He has no current or prior relationship with Scios.