# Two Deaths in Nesiritide Study Deemed Accidental

*The heart failure drug's safety has been in question since last March.*

BY MITCHEL L. ZOLER
*Philadelphia Bureau*

Safety concerns rose again for the heart failure drug nesiritide when the manufacturer, Scios, announced in early January that 2 additional patients had died in the nesiritide arm of a placebo-controlled trial with 237 patients.

The previously missed deaths, which were deemed to be accidental and unrelated to nesiritide treatment, were uncovered by Scios researchers who were working on a request from the Food and Drug Administration for an "expanded analysis" of the trial's results using an extended, 180-day follow-up of patients in the study.

Questions about the drug's safety first surfaced last March, when the published results of a metaanalysis suggested that patients with acute decompensated heart failure who were treated with nesiritide had an increased rate of worsening renal function. A second metaanalysis published last April further suggested increased mortality associated with nesiritide treatment. And last June, an expert panel of cardiologists assembled by Scios and led by Dr. Eugene Braunwald, Distinguished Hersey Professor of Medicine at Harvard Medical School, Boston, urged the company to run a new study to better define the safety and efficacy of nesiritide (Natrecor), compared with standard therapy. The panel also recommended that nesiritide use be limited to only its labeled indications and that Scios start a educational program to inform physicians about nesiritide's proper use.

The two previously missed deaths in nesiritide-treated patients were found in a study sponsored by Scios that was designed to assess the impact of nesiritide treatment on patients with acute decompensated heart failure who were treated in a hospital emergency department or observation unit. Efficacy measures included the need for hospital admission, the length of hospitalization, and the rate of rehospitalization during 30 days of follow-up. The study was done at 38 hospitals in the United States and was led by Dr. W. Franklin Peacock IV, an emergency medicine physician at the Cleveland Clinic.

**'The new numbers, 7 deaths in 120 nesiritide patients and 1 death in 117 placebo patients, border on statistical significance. But the numbers are small.'**

When the results from the study were published last October, the report said that 5 patients of the 120 who had received nesiritide had died within 30 days of treatment, compared with 1 patient out of 117 in the placebo group, a difference that was not statistically significant (J. Emerg. Med. 2005;29:243-52).

Both Dr. Peacock and Scios downplayed the significance of the two additional deaths, which also occurred during the first 30 days after treatment. Both deaths were accidental and not linked to nesiritide treatment. One patient died from carbon monoxide poisoning, and the second was in a traffic accident, said a spokeswoman for the Cleveland Clinic on behalf of Dr. Peacock.

The two additional deaths would not have changed the study's conclusions about nesiritide's safety, the spokeswoman added.

"Mortality was not the focus of the study, and detailed information about patient mortality was not collected," said Mark Wolfe, a spokesman for Scios.

This study "was unique in that patients were randomized in the emergency department. Therefore, I'm not entirely surprised that 30-day follow-up may not have been complete," commented Dr. Barry Massie, professor of medicine at the University of California, San Francisco, and chief of cardiology at the San Francisco Veterans Affairs Hospital.

"The new numbers, 7 deaths in 120 nesiritide patients and 1 death in 117 placebo patients, border on statistical significance. But the numbers are small and some of the deaths are most likely unrelated to treatment. Nonetheless, this finding does raise concern," said Dr. Massie. ■

# Levosimendan Fails to Impress in Acute Heart Failure Studies

BY BRUCE JANCIN
*Denver Bureau*

DALLAS — The investigational acute decompensated heart failure drug levosimendan garnered mixed reviews for its less-than-stellar performance in two large, multinational, double-blind, randomized clinical trials presented at the annual scientific sessions of the American Heart Association.

Levosimendan has both inotropic and vasodilator properties. But unlike other positive inotropes, whose action is mediated by increased intracellular calcium, levosimendan enhances cardiac myofilament sensitivity to an unchanged concentration of calcium. The drug also possesses peripheral vasodilator action mediated by an agonist effect on potassium channels.

**Intravenous diuretics will remain the initial intervention for patients who present with ADHF.**

**DR. PACKER**

Dr. Milton Packer reported on 600 patients in the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) trial who were hospitalized for acute decompensated heart failure (ADHF) not adequately responsive to intravenous diuretics. They were randomized to a 24-hour infusion of levosimendan or placebo along with intensification of standard background therapies as needed.

The primary end point in REVIVE II was a composite measure of clinical status during the first 5 days of hospitalization. The levosimendan group fared significantly better in this regard than did the controls, even though levosimendan had been stopped after the first 24 hours. Of those in the levosimendan arm, 76% showed moderate or marked improvement in a composite global assessment score, compared with 65% of controls. Fifteen percent in the levosimendan arm required rescue therapy because their condition worsened, compared with 26% in the placebo arm. Levels of brain natriuretic peptide—a surrogate for heart failure severity—were halved in the levosimendan group and stayed low. Levosimendan-treated patients felt better in as little as 6 hours, and that feeling persisted through 5 days.

On the other hand, 28 levosimendan-treated patients developed atrial fibrillation and 72 experienced ventricular arrhythmias, compared with 6 and 51, respectively, on placebo. Symptomatic hypotension and headaches were also more common with levosimendan. There were 49 deaths within 90 days with levosimendan and 40 with placebo, said Dr. Packer, professor of medicine and director of the Center for Biostatistics and Clinical Science at the University of Texas Southwestern Medical Center, Dallas.

He stressed that intravenous diuretics will remain the initial intervention for patients who present with ADHF. He estimated, however, that this therapy achieves an adequate response—relief of shortness of breath at rest—in only about half of the 3 million U.S. hospitalizations per year with ADHF as the primary or secondary diagnosis. It's in the other half where he sees levosimendan as potentially playing a major role.

Dr. Alexandre Mebazaa presented the results of the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study, the first large-scale study to examine the survival impact of medications used to treat ADHF. SURVIVE involved 1,327 patients in eight countries who were randomized to levosimendan or dobutamine along with standard background treatments.

The primary end point was 6-month all-cause mortality, which was 26% in the levosimendan arm and 28% with dobutamine, a nonsignificant difference. In hindsight, it was unrealistic to expect a mortality difference so long after a single 24-hour drug infusion, Dr. Mebazaa said. The results were more impressive closer to the treatment period. At day 5, for example, mortality was 4.4% in the levosimendan group and 6.0% with dobutamine, a 28% reduction in relative risk. As in REVIVE II, there was an increased incidence of atrial fibrillation with levosimendan, said Dr. Mebazaa, professor and director of the department of anesthesia and critical care medicine at Lariboisière Hospital, Paris.

Some attendees were enthused that the levosimendan trials had raised the bar in terms of the rigor with which ADHF drugs are evaluated. All currently available drugs were approved on the basis of hemodynamic gains rather than improved clinical status or outcomes.

Dr. Gordon F. Tomaselli, vice chairman of the AHA scientific sessions program committee, said in an interview that given the high lethality of ADHF and the very limited current treatment options, levosimendan "probably does have a place in the armamentarium."

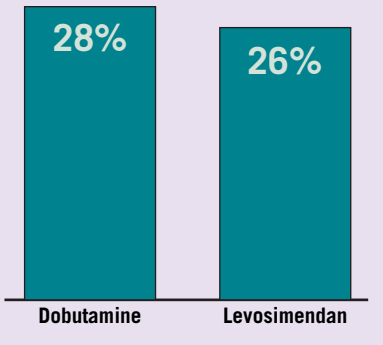
But Dr. Gregg C. Fonarow was skeptical, citing "clear safety concerns" he called "alarming."

"It's hard to conceive that with this dosing regimen this would be a treatment that physicians would want to use for their patients. A reduction in symptoms is not going to be acceptable if it comes at a price of substantial increased risk of severe adverse events," said Dr. Fonarow, professor of medicine at the University of California, Los Angeles, and director of the Ahmanson-UCLA Cardiomyopathy Center.

"If you compare the serious adverse events seen in REVIVE II with what was observed in the largest trial with nesiritide, levosimendan comes nowhere close to being as safe as nesiritide," he added. Nesiritide (Natrecor) has come under fire in the past year because of assertions it may worsen renal function and increase mortality.

Dr. Packer is a consultant to Abbott Laboratories and Orion Pharma, which funded REVIVE II and SURVIVE. Dr. Mebazaa is a consultant to Abbott. ■

**Six-Month Mortality in Acute Heart Failure Patients**




Note: Based on a study of 1,327 patients randomized to treatment.
Source: Dr. Mebazaa

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