Nesiritide's Safety in Heart Failure Questioned

Experts disagree on how to interpret two new metaanalyses and on how the drug should be used.

BY MITCHEL L. ZOLER
Philadelphia Bureau

Experts are divided over nesiritide's safety in patients with acute decompensated heart failure after two metaanalyses suggested a single dose might worsen renal function and increase mortality in the first 30 days after treatment.

Concern was strong enough to prompt Johnson & Johnson, which markets nesiritide (Natrecor), to revise its labeling for the drug the same week that the second study (the one reporting an adverse mortality effect) was published (JAMA 2005;293:1900-5). The new labeling expanded the section headed "Effect on Mortality" with the company's own metaanalysis, which included more studies than the published report and showed a less alarming trend toward increased deaths among the patients who received nesiritide.

Johnson & Johnson also began to assemble a pair of expert panels to review available data and recommend future studies.

Experts differed on what the new analyses mean, what danger nesiritide might pose, and how the drug should be used in the immediate future. Some said enough questions were raised by the new findings to warrant making nesiritide a second-line treatment, at least until additional safety data are collected. Others said nesiritide remains a valuable option for patients with acute decompensation and that the drug should stay in the front-line of therapy until clear-cut evidence of danger is found.

The one point everyone agreed on was that the studies so far had not been designed to assess nesiritide's impact on survival, and thus any decisions now must be tentative, pending future findings.

"The implications of the [JAMA] paper's conclusions are that there are limited data with which to judge the safety of nesiritide at the FDA-approved dosages, and that the data that exist suggest the possibility of increased mortality with nesiritide treatment. I concur with the recommendation [of the paper's authors] to use nitroglycerin [before using nesiritide] in appropriate patients," said John R. Teerlink, M.D., director of the heart failure clinic at the Veterans Affairs Medical Center in San Francisco. Dr. Teerlink receives speaking fees from GlaxoSmithKline Inc., which owns the European rights to nesiritide.

"I don't agree with the conclusion regarding the use of nesiritide. The analysis was limited by a small number of patients and by studies that were not designed to look at mortality. I think there need to be mortality studies that look at nesiritide, as well as nitroglycerine, nitroprusside, milrinone, and dobutamine," the other drugs used to treat acute decompensation, said Uri Elkayam, M.D., director of the heart failure program at the University of Southern California in Los Angeles. "None of these drugs have had their safety tested" in this clinical setting, he said in an interview. Dr. Elkayam has received research support from Johnson & Johnson and is a consultant to and speaker for the company regarding nesiritide.

The first of the metaanalyses examined the possibility of a link between worsening renal function and nesiritide treatment. Jonathan D. Sackner-Bernstein, M.D., and his associates combined the findings from five randomized, controlled, double-blind studies that tested nesiritide in patients with acute decompensated heart failure and that reported the drug's effect on renal function. A significant effect on the kidney was defined as a rise in serum creatinine of more than 0.5 mg/dL following single-dose treatment.

In this combined analysis, the 797 patients who were treated with nesiritide included 21% who had worsening renal function, compared with a 15% rate among the 472 patients who were treated with comparator drugs (a diuretic, a vasodilator, or an inotrope), a statistically significant difference (Circulation 2005;111:1487-91).

The second metaanalysis, published 3 weeks later in JAMA, combined findings from three randomized, double-blind parallel group studies. In these, mortality during 30 days of follow-up was reported, nesiritide was administered as a single infusion for at least 6 hours, and inotropic therapy was not mandated in the control group. To produce intention-to-treat data, the metaanalysis included nine patients who had been excluded from the original safety analysis of one of these three studies because they had never received nesiritide.

Of 485 patients treated with nesiritide, 7.2% died within 30 days of treatment, compared with a 4.0% mortality rate among 377 patients treated with a comparator drug. This difference did not reach statistical significance.

The authors emphasized that their finding was "hypothesis generating rather than conclusive evidence of harm."

"The best data suggest that [nesiritide] is likely to be associated with an increased risk of death after its use, all for a modest reduction in symptoms of shortness of breath for up to 6 hours, compared to placebo," said Dr. Sackner-Bernstein, director of heart failure and preventative research at North Shore University Hospital, Manhasset, N.Y., in an interview. Dr. Sackner-Bernstein receives grant support, honoraria, and consulting fees from GlaxoSmithKline.

"Physicians have adopted nesiritide widely because they believe that it improves outcomes beyond the transient improvement in dyspnea that led to its approval," said Barry Massie, M.D., chief of cardiology at the VA Medical Center, San Francisco.

The two articles by Dr. Sackner-Bernstein and associates "dispel the belief that nesiritide is beneficial with regard to renal function and survival. Given the potentially increased risk of mortality and worsening renal failure, it makes sense to use it only in patients who have not responded to usual therapies." Dr. Massie receives consultant fees from GlaxoSmithKline and from Scios, the division of Johnson & Johnson responsible for nesiritide.

The Food and Drug Administration was also unconvinced by the metaanalyses done by Dr. Sackner-Bernstein.

"The data currently available are not materially different than when the cardiorenal advisory committee [of the FDA] discussed them prior to [nesiritide's] approval. In fact, the advisory committee was so unimpressed with the slightly adverse lean that they recommended not saying anything about mortality in the label," an FDA spokeswoman said.

"The problem with metaanalyses is that the contribution each study makes is known when you are deciding what studies to combine. There is no way to compensate for the biases this introduced," she said.

"Dr. Sackner-Bernstein and colleagues made a reasonable set of choices, but other reasonable alternatives are also possible. Most other combinations of studies will yield an estimate of risk lower than the one in their paper," she noted.

That was exactly what Johnson & Johnson found when it ran its own metaanalysis of the seven controlled studies of nesiritide in which 30-day mortality was tallied. In this analysis, which was one of two that they added to the drug's labeling in April—the other analysis looked at 180-day mortality in four studies—the 30-day death rate was 5.3% in 1,059 patients treated with nesiritide and 4.3% among 658 patients treated with a comparator drug.

According to a rebuttal of the JAMA metaanalysis released by Johnson & Johnson in April, "the recently published metaanalysis is a selective reinterpretation of existing published data. If all available mortality data for all Natrecor [nesiritide] trials are taken together, Natrecor treatment does not significantly increase the risk of mortality, particularly after adjustment for baseline differences."

But Dr. Sackner-Bernstein defended his group's more selective approach. "The metaanalysis we performed is more relevant. Our metaanalysis focused on the patients for whom the drug is intended, in studies that were randomized and double-blind and performed in a more rigorous fashion," he told this newspaper.

Despite Johnson & Johnson's contention that the nesiritide database doesn't indicate a mortality problem, in April the company picked Eugene Braunwald, M.D., chairman of the Thrombosis in Myocardial Infarction (TIMI) study group at Brigham and Women's Hospital in Boston, to head an advisory panel that will review nesiritide's mortality data and advise the company on how to design additional mortality studies. Dr. Elkayam was named to head a similar panel that will review the effects of nesiritide on renal function. ■

Decompensation: A Changing Paradigm

The controversy about nesiritide's safety comes when some heart failure experts are crafting a new understanding of acute decompensated heart failure and how it is best managed.

"This is a complex syndrome, and patients can be very different," Mihai Gheorghiade, M.D., said in an interview. "Treatment must be tailored to the clinical presentation."

Recent observations from a pair of registries that together have more than 150,000 patients with acute decompensated heart failure have shown that these patients fall into three categories based on their systolic blood pressure. About 50% of patients are hypertensive (systolic pressure more than 140 mm Hg); about 48% are normotensive; and about 2% are hypotensive (systolic pressure less than 90 mm Hg).

Hypertensive patients should initially be treated with a vasodilator drug such as nesiritide or a nitrate, said Dr. Gheorghiade, associate chief of cardiology at Northwestern University in Chicago. Normotensive patients can initially receive either a diuretic or a vasodilator.

Another way to distinguish acute decompensated patients is by the clinical events that led to their acute state. One pathway is marked by chronic congestion that gradually builds over days or weeks to high pulmonary capillary wedge pressure and leg edema. The second pathway involves rapid-onset fluid overload triggered by high blood pressure (vascular failure). This may result from neurohormonal activation and increased sympathetic tone that raises blood pressure and redistributes blood from the systemic to the pulmonary circulation.

Patients with gradual-onset fluid overload tend to be normotensive or hypotensive, and it makes sense to initially treat them with a diuretic. Patients with rapid-onset fluid redistribution tend to be hypertensive, and the best initial therapy is with a vasodilator, Dr. Gheorghiade said. In patients with a rapid fluid shift, the goal is to quickly lower blood pressure without losing too much fluid.

Results of the major study that compared nesiritide against another vasodilator, nitroglycerin, the Vasodilation in the Management of Acute Congestive Heart Failure study, showed that although the two drugs had similar effects on systolic blood pressure, nesiritide treatment worked faster and better than nitroglycerin for reducing pulmonary capillary wedge pressure, he said (JAMA 2002;287:1531-40).

Recently, a new name for acute decompensation, "cardiovascular renal insufficiency," was coined by Dr. Gheorghiade and Marvin Konstam, M.D., chief of cardiology at Tufts-New England Medical Center in Boston. They hope the new name will guide physicians to the important therapeutic targets of the condition, and help establish a new identity for the syndrome as its critical clinical features become better defined.