Conivaptan Reverses Hyponatremia, Studies Show

ARTICLES BY
MITCHEL L. ZOLER
Philadelphia Bureau

NEW ORLEANS — Conivaptan was safe and effective for treating hyponatremia in three phase III studies that together involved about 200 evaluable patients.

Based in part on these findings, the Food and Drug Administration issued an approvable letter for conivaptan last December. According to Yamanouchi Pharma America, the company that developed the drug and sponsored the studies, the FDA said that it will license conivaptan for the treatment of hyponatremia if the company provides additional safety data and meets certain other conditions.

Currently, no agent has FDA approval for treating hyponatremia, which affects 2%-3% of all hospitalized patients and is more prevalent among patients with advanced heart failure and in the elderly. Hyponatremia is defined as a serum sodium concentration of less than 136 mEq/L, and is usually managed by restricting fluids.

Conivaptan is an antagonist for the arginine vasopressor receptor. The drug causes aquaresis and reduces vasomotor tone. Patients with heart failure often have abnormally high levels of arginine vasopressin, which promotes water reabsorption and helps produce the edema that often accompanies heart failure. Conivaptan can be given either orally or intravenously, however, Yamanouchi is only seeking approval for intravenous administration.

Results from the three studies were presented in posters at the annual scientific sessions of the American Heart Association. One study included 74 men and women least 18 years old with a serum sodium level of 115-130 mEq/L who were either hypervolemic or euvolemic. About 43% of the patients had hyponatremia secondary to heart failure, about 20% had idiopathic hyponatremia, and in the rest it was due to other factors. About 74% of the patients were euvolemic.

In three phase III studies, conivaptan increased serum sodium levels significantly more than placebo after less than a week of treatment.

Patients were randomized to treatment with 20 mg conivaptan orally b.i.d, 40 mg orally b.i.d, or placebo, and treatment continued for 5 days. Three patients dropped out during the study, one from each group.

During the 5 days of treatment, serum sodium levels increased in the conivaptan group in a dose-related manner and to levels that were significantly above those reached in the control group, reported Jala K. Ghali, M.D., director of clinical research at Cardiology Centers of Louisiana in Shreveport. The 20-mg b.i.d dosage boosted sodium levels from a mean of 125 mEq/L at baseline to about 132 mEq/L after 5 days. The 40-mg b.i.d. dosage raised sodium levels from a mean of 125 mEq/L at baseline to about 133 mEq/L after 5 days. In the placebo group, the starting sodium level averaged 124 mEq/L, which rose to about 127 mEq/L after 5 days.

Conivaptan was effective regardless of whether patients were euvolemic or hypervolemic at baseline, and regardless of the etiologic cause of hyponatremia. Both dosages were well tolerated; the rate of drug-related adverse events was similar in the three treatment groups, Dr. Ghali reported.

The second study reported at the meeting was very similar in design to the first, except that conivaptan was administered intravenously.

The study initially treated 84 patients, of whom 66 completed a 4-day course of treatment. The study enrolled adult men and women with a baseline serum sodium level of 115-130 mEq/L. Two thirds of the patients were euvolemic, and 30% had heart failure as their etiology of hyponatremia. Patients were randomized to treatment with 40 mg/day conivaptan intravenously, 80 mg/day, or placebo.

After 4 days of treatment, serum sodium levels had increased significantly in both treatment groups, compared with the control patients, reported Joseph G. Verbalis, M.D., professor of medicine and chief of the division of endocrinology and metabolism at Georgetown University, Washington. Once again, the increases were dose dependent, and were very similar to those seen with oral dosing. And conivaptan was effective whether patients were euvolemic or hypervolemic, and regardless of the etiology of their hyponatremia.

Both dosages of the intravenous drug were well tolerated. Although the incidence of drug-related adverse effects were more than twice as common in patients treated with conivaptan, compared with those who received placebo, the effects were mild to moderate, Dr. Verbalis said. Discontinuations due to adverse effects were similar in all treatment groups.

The third study resembled the first oral-administration study, but was run in Europe. It enrolled 89 patients, of whom 72 completed the 5-day treatment. It included adult men and women with serum sodium levels of less than 130 mEq/L. About 58% of the patients were euvolemic at baseline, and 30% had heart failure as their cause of hyponatremia. Patients were randomized to receive 20 mg oral conivaptan b.i.d, 40 mg b.i.d., or placebo.

After 5 days of treatment, serum sodium levels were significantly higher in both treatment groups, compared with control patients, said Peter Gross, M.D., professor of medicine and nephrology at the Carl Gustav Carus University Clinic in Dresden, Germany. Sodium levels rose in a dose-dependent fashion, and the increases were similar to those seen in the two U.S. studies. The effects on sodium levels were similar regardless of volemic status at baseline and hyponatremia etiology. Conivaptan was well tolerated, with a low rate of drug-related adverse effects and few discontinuations due to adverse effects. ■

Chronic Methamphetamine Use Appears to Be Cardiotoxic

NEW ORLEANS — Chronic use of methamphetamine can lead to nonischemic, dilated cardiomyopathy and profound left-ventricular dysfunction, according to a study of 53 methamphetamine users seen at a single medical center in California.

"To our knowledge, this is the first study of its type to examine the relationship between chronic methamphetamine use and its effect on the heart," Melissa R. Robinson, M.D., reported in a poster at the annual scientific sessions of the American Heart Association.

"In contrast with cocaine, long-term methamphetamine use seems to have a direct, cardiotoxic effect, and promotes the development of severe, nonischemic, dilated cardiomyopathy," said Dr. Robinson of the department of internal medicine at the University of California, Davis. Although the number of chronic users of methamphetamine is not known, a 2001 survey estimated that more than 5 million people in the United States had tried the drug, she said.

Her review started with 226 patients who were either hospitalized at the UC Davis Medical Center or seen in its emergency department during 1993-2002 and reported using methamphetamine and were diagnosed with either cardiomyopathy or heart failure. This list of patients was then pared to exclude those with another possible explanation for their heart disease, including a history of significant alcohol use (at least four drinks per day for at least 5 years), alcoholic cirrhosis, cocaine use, or severe coronary artery disease.

This left 53 methamphetamine-using patients who had no clear etiology for their cardiomyopathy or heart failure. Their average duration of drug use was 5 years.

Their average age was 46 years, and 43% were younger than 45. Their average left-ventricular end-diastolic dimension was 66.3 mm, and 87% had an end-diastolic dimension of more than 55 mm, indicating severe dilated cardiomyopathy. Echocardiography was done on 46 patients, who had an average left-ventricular ejection fraction of 25%; 35 of the 46 patients (76%) had an ejection fraction of less than 30%.

Several of the patients had severe complications while they were followed at UC Davis. Five patients had strokes, another five had recurrent ventricular arrhythmias that required implantation of a cardioverter defibrillator, and six had sudden deaths. Four patients had resolution of their cardiomyopathy after ceasing methamphetamine use.

"These clinical findings were unusual given the relatively young age of these patients," Dr. Robinson said. ■

Low Relative Lymphocyte Count Flags Cardiomyopathy Risk

NEW ORLEANS — A depressed relative lymphocyte count was associated with an increased risk of death in patients with hypertrophic cardiomyopathy in a study with 962 patients.

The relative lymphocyte count (RLC) is an inexpensive, universally available test "that may be helpful in identifying patients with hypertrophic cardiomyopathy who have a worse prognosis," Steve R. Ommen, M.D., said while presenting a poster at the annual scientific sessions of the American Heart Association.

"The relative lymphocyte count is part of the standard complete blood count, and involves no incremental cost," added Dr. Ommen, a cardiologist at the Mayo Clinic in Rochester, Minn. A depressed RLC is a marker of systemic stress, and the results from prior studies have linked the marker to adverse outcomes in patients with other cardiovascular disease states.

Dr. Ommen and his associates reviewed case records for patients with hypertrophic cardiomyopathy who were seen at Mayo during 1994-2003. Patients were selected who had received a complete blood count within 1 week of their clinical evaluation.

RLC is the fraction of all leukocytes that are lymphocytes, expressed as a percent. The normal range is 20%-47%.

Among the 962 patients with hypertrophic cardiomyopathy, 258 (27%) had an RLC that was below normal. The mean RLC in this group was 14%.

During follow-up, which ranged from 1 month to 9.6 years (mean 1.8 years), the average mortality during the first year of follow-up was 3% in patients with a normal RLC, compared with 12% in those with a depressed RLC. During the first 5 years of follow-up, the average death rate was 15% in the group with a normal RLC at baseline, compared with 40% in those with a low RLC.

In a multivariate analysis that controlled for possible confounding clinical and demographic factors, three parameters were associated with a statistically significant increase in risk of death: increased age; atrial fibrillation, which boosted the risk of death 3.3-fold; and a depressed RLC, which raised the relative risk of death 2.1-fold, Dr. Ommen said.