Conivaptan Shown to Reverse Hyponatremia

BY MITCHEL L. ZOLER
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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 developing the drug, the FDA said that it will license conivaptan for the treatment of hyponatremia if Yamanouchi provides additional safety data and meets certain other conditions. Yamanouchi sponsored the phase III studies.

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.

In efficacy trials, serum sodium levels increased in the conivaptan group in a dose-related manner to levels significantly above those in the controls.

Conivaptan is an antagonist for the arginine vasopressor receptor. Through this activity, 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 administered either orally or intravenously; however, Yamanouchi is only seeking approval to market conivaptan with 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 at 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 remainder it was due to other factors. About 74% of the patients were euvolemic.

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 treatment 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 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 also 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 in severity, Dr. Verbalis said. Discontinuations due to adverse effects were similar in all three treatment groups.

The third study closely resembled the first oral-administration study, but it was run in Europe. It enrolled 89 patients, of whom 72 completed the 5-day treatment. This study enrolled 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.

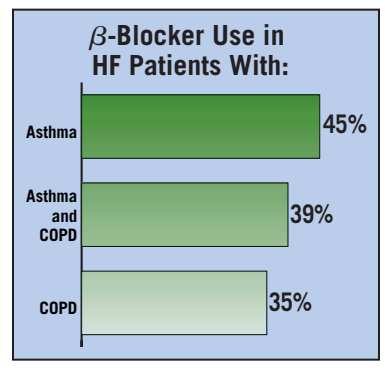
After 5 days of treatment, serum sodium levels were significantly higher in both treatment groups, compared with control patients, said Peter Gross, M.D., professor of medicine and nephrology at the Carl Gustav Carus University Clinic in Dresden, Germany. Sodium levels rose in a dose-dependent fashion, 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. Treatment with conivaptan was well tolerated, with a low rate of drug-related adverse effects and few discontinuations due to adverse effects. ■

β-Blockers Appear Safe in HF Patients With Lung Disease

BY DOUG BRUNK
San Diego Bureau

SEATTLE — The long-term use of β-blockers in heart failure patients with chronic obstructive pulmonary disease and/or asthma did not increase the risk of respiratory complications, results from a large retrospective study have shown.

"Although a history of asthma and/or COPD is still considered a relative contraindication to the use of β-blockers in the management of [heart failure], our study found that long-term use did not increase the risk for respiratory complications," Jay I. Peters, M.D., said at a press briefing during the annual meeting of the American College of Chest Physicians. "We did not see any differences in outcome with the use of cardioselective vs. noncardioselective β-blockers. The proven mortality benefit of β-blocking medication in [heart failure] mandates their use whenever possible."



During the 1960s, physicians viewed β-blockers as contraindicated in patients with HF. "Subsequent research revealed that the use of cardioselective β-blockers upregulated the β-receptor and was useful" in patients with HF, said Dr. Peters of the division of pulmonary diseases and critical care medicine at the University of Texas Health Science Center at San Antonio.

In fact, studies have shown improved survival among HF patients on β-blockers: For every 20 patients treated with these drugs, one life is saved (Ann. Intern. Med. 2001;134:550-60; N. Engl. J. Med. 2001;344:1711-2).

"Unfortunately, many review articles and guidelines often list asthma and COPD as relative contraindications to using β-blockers. Many physicians in the community are hesitant to use these medications if the patient has any history of obstructive lung disease," he noted.

A recent metaanalysis of data on 141 patients concluded that cardioselective β-blockers are not associated with increased respiratory symptoms or inhaler use, and that β-blockers may enhance the effect of inhaled β-agonist (Cochrane Database Syst. Rev. 2002;4:CD002992). But "the duration of the studies was only 3 days to 4 weeks, and only 46 patients had pulmonary function tests," Dr. Peters said.

In a study funded by the U.S. Department of Defense, he and his associates evaluated the prevalence of β-blocker use and the prevalence of respiratory events in patients with COPD and/or asthma. Their retrospective analysis of prospectively collected data included 1,067 patients with HF who were followed over 18 months. Investigators reviewed every nonroutine office visit, ER visit, and hospitalization over the 18-month period to evaluate respiratory symptoms and cardiac symptoms.

The prevalence of asthma was 5.9%, and that of COPD was 11.2%; 2.5% of patients had both COPD and asthma. "Overall, 19.6% of patients had obstructive lung disease and could have benefited from β-blockers," he said.

Only 39% of patients with asthma and COPD were on β-blockers. About 45% of asthmatics and 35% of patients with COPD were on β-blockers. In addition, 49% of the patients were prescribed cardioselective β-blockers "that are felt to be safer in patients with obstructive lung disease."

Patients with HF and any respiratory diagnosis had a threefold increase in respiratory encounters, compared with patients who had a diagnosis of HF alone.

Overall, the use of β-blockers in patients with asthma and/or COPD did not increase the number of respiratory encounters in terms of unscheduled office visits, ER visits, or hospitalizations.

β-Blocker use in patients with asthma and COPD statistically lowered the rate of respiratory events, he noted, "but the number of patients in this group was small, and larger studies will be needed to confirm this finding." ■

LVAD Placement Credentials Defined

A new certification program for the implantation of left ventricular assist devices was released for review by the Joint Commission on Accreditation of Healthcare Organizations.

The certification will be conducted within the Disease-Specific Care Certification program. Organizations seeking certification will have to meet the standards, practice guidelines, and performance measurements of the specific-care program, as well as left ventricular assist device (LVAD)–specific requirements based on those used in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, according to the Association for the Advancement of Medical Instrumentation (AAMI). The AAMI expects the requirements to be ready for Centers for Medicare and Medicaid Services review by April.

—Mark Lesney