Conivaptan Shown to Reverse Hyponatremia

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 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.

Conivaptan is an antagonist for the argin­nine vasopressin type 1A 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 reab­ sorption 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 intra­venously.

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 eu­volemic or hypervolemic, and regardless of the 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 director of the division of pulmonary and critical care medicine 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 events 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, except that the increases were more similar to those seen in the two phase II studies. 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 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.

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conivaptan was well tolerated, with a low incidence of adverse effects. About 74% of the patients were euvolemic, and 30% had heart failure as their etiology of hyponatremia. 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.

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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 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.

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 (JCAHO). 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 with Cardiac Insuffi­ciency (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

β-Blockers Appear Safe in HF Patients With Lung Disease

BY DOUG BRUNK
San Diego Bureau

SEATTLE — The long-term use of β­blockers in heart failure patients with chronic obstructive pulmonary disease (COPD) 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 β­blockers in the management of [heart failure], our study found that long­term use did not increase the risk for respiratory complications,” Jay L. 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 β­blockers. The proven mortality benefit of β­blocking medica­tion [in [heart failure]] mandates their use whenever possible.”

During the 1960s, physicians viewed β­blockers as contraindicated in patients with HF. “Subsequent research re­vealed that the use of cardioselective β­blockers upregulated the β­receptor 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 β­blockers. 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 β­blockers. 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 β­blockers are not associated with increased respiratory symptoms or inhaler use, and that β­blockers may enhance the effects of inhaled β­agonist (Cochrane Database Syst. Rev. 2002;4:CD002992). But “the duration of the studies was only 3 days to 4 weeks, and only the pre­dominant function tests,” Dr. Peters said.

In a study funded by the U.S. De­partment of Defense, he and his asso­ciates evaluated the prevalence of β­blocker 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 9.9%, 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,” said Dr. Peters, who be­lieved that β­blockers might have benefitted from β­blockers,” he said. Only 39% of patients with asthma and COPD were on β­blockers. About 45% of asthmatics and 35% of pa­tients with COPD were on β­blockers. In addition, 49% of the patients were prescribed cardioselective β­blockers “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 β­blockers 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.

β­Blocker 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.”

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