Albuterol Found Ineffective in Acute Lung Injury

BY ROBERT FINN

SAN FRANCISCO — A placebo-controlled clinical trial of albuterol in acute lung injury was terminated after the first interim analysis showed that the beta-2 agonist was no better than placebo.

The data and safety monitoring board (DSMB) found that patients given aerosolized albuterol had no improvement in ventilator-free days or 60-day mortality, Dr. Michael A. Matthay reported at a meeting on critical care medicine sponsored by the University of California, San Francisco.

Dr. Matthay of UCSF said there were good reasons to suspect that beta-2 agonist therapy would be beneficial in acute lung injury (ALI). In preclinical studies, the therapy increased the resolution of alveolar edema by promoting sodium and chloride transport, and reduced lung vascular permeability. In a clinical trial, ALI patients treated intravenously with salbutamol had lower lung water levels.

The ALTA (Albuterol for the Treatment of ALI) trial used aerosolized albuterol because observational studies suggested that therapeutic levels of albuterol could be achieved in the pulmonary edema fluid of ALI patients. The drug does not simply deposit in the airways.

All patients had a P/F (arterial oxygen pressure to fraction of inspired oxygen ratio, or PaO_2 to FiO_2 ratio) below 300 mm Hg, bilateral infiltrates, and no clinical evidence of left atrial hypertension. The patients were receiving positive pressure ventilation via endotracheal tube. Patients were excluded if they had moderate to severe liver disease, moderate to severe chronic obstructive pulmonary disease, chronic or acute need for beta agonists, or acute myocardial infarction within 30 days. Patients were given aerosolized albuterol at 5 mg/2.5 mL, or 2.5 mL of normal saline, every 4 hours until day 10 or until 24 hours after extubation. The albuterol dose was reduced to 2.5 mg/2.5 mL if the patient developed tachycardia or arrhythmia.

At the time the DSMB terminated the trial, 282 patients had been enrolled. There were no significant differences between albuterol and placebo groups on any baseline demographic or laboratory measurement, including Acute Physiology and Chronic Health Evaluation (APACHE) III score, number of organ failures, tidal volume, type of primary lung injury, electrolytes, blood pressure, and central venous pressure.

The investigators found that plasma albuterol levels were in the expected range in virtually all patients who were assessed.

The study's primary outcome was the number of ventilator-free days within 28 days after admission. Patients receiving albuterol had a mean of 14.5 ventilator-free days versus 16.5 days for control patients. A secondary outcome was 60-day mortality, which was 23% among patients taking albuterol and 17.7% among control patients. Neither of those differences was statistically significant.

The investigators found no evidence of albuterol's effectiveness in any subgroup analysis, including analyses limited by gender, in patients with P/F below 200 mm Hg, and in patients with or without shock.

Dr. Matthay, who was the principal investigator of the ALTA trial, suggested three possible reasons that albuterol did not perform as expected.

It could be that the alveolar epithelium may have been too injured to respond to beta agonist therapy. The aerosol route could have delivered inadequate levels of albuterol to the injured alveoli. Or conservative fluid management and lower tidal volume ventilation might have reduced lung injury and lung water to the extent that any additional fluid clearance with albuterol therapy had no beneficial effect.

Dr. Matthay said that he had no conflicts of interest to disclose. The ALTA study was supported by the National Heart, Lung, and Blood Institute. ■

Omega-3 Supplements Not Helpful in Acute Lung Injury

BY ROBERT FINN

SAN FRANCISCO — A placebo-controlled trial of omega-3 fatty acid food supplements in patients with acute lung injury or acute respiratory distress syndrome was terminated early when an interim analysis showed that mortality was worse in patients taking the supplements.

Within 60 days, 27% of patients taking omega-3 fatty acids had died, versus 16% of controls, a significant difference, Dr. Michael A. Matthay said at a meeting on critical care medicine sponsored by the University of California, San Francisco. Patients taking the supplements also had fewer ventilator-free days within 28 days (14.6 days versus 17.4 days for controls) and fewer ICU-free days within 28 days (13.9 days versus 16.8 days for controls).

"There were some phase II data indicating that maybe omega-3s would be beneficial in these patients," said Dr. Matthay of UCSF. "It's a sobering result, for sure."

The study was part of a trial called EDEN-Omega (Early vs. Delayed Enteral Feeding and Omega-3 Fatty Acid/Antioxidant Supplementation for Treating People With Acute Lung Injury or Acute Respiratory Distress Syndrome), which was intended to test both omega-3 supplementation and early versus delayed enteral feeding. Although the data safety and monitoring board terminated the omega-3 arm of the study after 272 patients had been recruited, the enteral feeding arm is ongoing.

Patients had a P/F (arterial oxygen pressure to fraction of inspired oxygen ratio, or PaO_2 to FiO_2 ratio) below 300 mm Hg, bilateral infiltrates, a requirement for positive pressure ventilation via endotracheal tube, and no clinical evidence of left-sided cardiac failure. Patients were excluded for severe liver disease, severe chronic respiratory disease, and other reasons. Patients were randomized to receive either full-calorie enteral feeding or full-calorie enteral feeding plus twice-daily supplementation with omega-3 fatty acids, gamma linolenic acid, and antioxidants. The supplements were continued for 21 days or until mechanical ventilation was no longer required.

At study termination, the increase in 60-day mortality in the supplement group just reached significance ($P = .05$). The differences in ventilator-free days and ICU-free days were somewhat more certain (P values of .03 and .02). "One can argue about whether there was enough power here to conclude for sure that [omega-3 fatty acid] was deleterious, but it's certainly strongly in that direction," Dr. Matthay said.

Dr. Matthay stated that he had no conflicts of interest to declare. The study was supported by the National Heart, Lung, and Blood Institute. ■

© CLAYTON HANSEN/ISTOCKPHOTO

At 60 days, 27% of patients taking omega-3 fatty acids had died, versus 16% of controls.

Rise in Prevalence of Asthma As a Secondary Diagnosis

BY HEIDI SPLETE

WASHINGTON — The prevalence of asthma as a principal reason for hospitalization has remained steady, but its prevalence as a secondary diagnosis has increased by 113% in hospitalized adults and by 54% in hospitalized children, based on approximately 9 years of data from two large databases.

The number of adult hospital stays with asthma as a secondary diagnosis rose from 753,800 in 1997 to nearly 1.5 million in 2005. (For 2006, the number was estimated at slightly more than 1.6 million, based on incomplete data.) The number of pediatric hospital stays with asthma as a secondary diagnosis rose from 128,300 in 1997 to 197,000 in 2006.

The five most common reasons for hospital stays in 2006 in adults with asthma as secondary diagnosis were pneumonia (6.6%), heart failure (3.9%), nonspecific chest pain (3.8%), osteoarthritis (3.3%), and mood disorders (3.3%). The five most common reasons for hospital stays in children with asthma as a secondary diagnosis were pneumonia (27%), acute bronchitis (8.8%), mood disorders (5.5%), appendicitis (2.7%), and fluid and electrolyte disorders (2.4%), reported Chaya Merrill, M.P.H., Dr.P.H., of Thomson Reuters, and her colleagues.

They reviewed data from the Healthcare Cost and Utilization Project (HCUP), a collection of databases supported by the Agency for Healthcare Research and Quality. The results were presented in a poster at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

The data for the study were obtained from the Nationwide Inpatient Sample (NIS), which includes 90% of adult hospitalizations, and the Kids' Inpatient Database (KID), which represents 80% of pediatric hospitalizations.

In adults, the hospitalizations involving asthma as either a primary or secondary diagnosis were highest in those aged 65 years and older. Overall, hospitalization rates rose with increasing age, starting at 18 years.

In children, hospitalizations involving asthma as a primary or secondary diagnosis were highest in those younger than 1 year (about 8 per 1,000 children) and lowest among those aged 15-17 years (about 2 per 1,000 children).

In adults, average rates of hospitalization with asthma as a secondary condition were highest in the Northwest and Midwest, and were lower in the South and West (10.6, 8.7, 6.9, and 6.0 stays per 1,000 persons, respectively). In children, average rates of hospitalization with asthma as a secondary condition were 3 stays per 1,000 persons in the Northeast, Midwest, and South, and 2 stays per 1,000 persons in the West.

For both adults and children, rates of hospitalization with asthma as either a primary or secondary diagnosis were higher in communities with a median income of $38,000 or less than in wealthier communities, the researchers noted.

The study was sponsored by the Agency for Healthcare Research and Quality, a branch of the United States Department of Health and Human Services. ■

Pages 4a—4b