Silver-Coated Tracheal Tubes Reduce Pneumonia

BY MARY ANN MOON
Contributing Writer

Endotracheal tubes coated with silver, which has shown potent broad-spectrum antimicrobial activity in vitro, reduced the incidence of ventilator-associated pneumonia by 35% in a multicenter study, researchers reported.

"This is the first intervention demonstrated to reduce ventilator-associated pneumonia [VAP] incidence that does not require more effort or supervision from clinicians providing bedside care," said Dr. Marin H. Kollef of Washington University, St. Louis, and associates.

However, the reduced rate of pneumonia did not translate into decreased mortality, duration of intubation, duration of ICU stay, duration of hospitalization, or frequency or severity of the adverse effects of intubation.

In an editorial comment, Dr. Jean Chastre said that physicians should "probably" consider using silver-coated endotracheal tubes for "the subset of patients at very high risk of developing early-onset VAP, such as neurologically impaired patients or trauma patients." But the value of the device for other patients, particularly those who might need prolonged ventilation, has not yet been shown.

Dr. Kollef and associates compared the silver-coated endotracheal tube with standard tubes in a prospective trial sponsored by the device manufacturer, C.R. Bard Inc. A total of 1,509 patients requiring mechanical ventilation for 24 hours or longer were treated at 54 medical centers.

Microbiologically confirmed VAP developed in 4.8% of patients using the silver-coated tube, compared with 7.5% of those using the standard tube—a relative risk reduction of 35.9% and an absolute risk reduction of 2.7%.

The number of patients needed to be treated with the silver-coated tube to prevent one case of VAP was 37, the investigators said (JAMA 2008;300:805-13).

The device appeared to be most effective in preventing VAP during the first 10 days of intubation, "which is clinically relevant because the median duration of intubation is less than 10 days, and more than 75% of patients are extubated before 10 days," Dr. Kollef and colleagues said.

Mortality was not significantly different between patients who used the silver-coated tube (30%) and those who used standard tubes (27%). There also were no significant differences between the two groups in duration of intubation, ICU stay, or hospital stay, or in the frequency and severity of adverse events related to endotracheal intubation.

This lack of between-group differences might have been related to the unusually low rate of VAP in the control group, which was approximately half of the expected rate of 15%, the investigators noted.

In his editorial comment, Dr. Chastre of the University of Pierre and Marie Curie, Paris, noted that more than 7,000 potential subjects were screened but not enrolled in the trial because they were unable to provide informed consent within the time frame necessary for emergency intubation or were unlikely to require intubation for 24 hours or longer. This threatens both the external validity of the trial and its clinical relevance, he said.

Moreover, the number of cases of VAP was so low that the addition of only three cases among patients using the silver-coated tube "would have sufficed to render the trial statistically inconclusive," Dr. Chastre wrote (JAMA 2008;300:842-4).

In addition, there was a statistically significant imbalance in the proportion of patients who had preexisting chronic obstructive pulmonary disease between the two groups, which favored the group using the silver-coated tube. And the number of cases of late-onset VAP—pneumonia developing after 7 days of mechanical ventilation—was so small that it limited the study's ability to show efficacy with prolonged intubation.

"Consequently, silver-coated tubes should not be viewed as the definitive answer for VAP prevention, and, until additional data confirm the clinical effectiveness and cost benefit of these devices, their use should be restricted to high-risk patients" in ICUs with low background infection rates, Dr. Chastre noted.

All the authors of this study received grant support from Bard, and Dr. Kollef and Dr. Chastre have received fees from other companies. ■

FDA Panel Reviews Pneumonia Indications for Doripenem

BY ELIZABETH MECHCATIE
Senior Writer

ROCKVILLE, MD. — A Food and Drug Administration advisory panel was split on whether the efficacy and safety data on doripenem, an injectable, broad-spectrum antibiotic, were adequate to support its approval for treating nosocomial pneumonia including ventilator-associated pneumonia.

At a meeting of the FDA's Anti-Infective Drugs Advisory Committee, the panel voted 7 to 6 that the clinical efficacy data from two noninferiority studies comparing doripenem with other antibiotics supported approval of the drug for this indication. The panel voted 8 to 5 that doripenem was safe for treating patients with nosocomial pneumonia including ventilator-assisted pneumonia (VAP) based on the trial data.

Johnson & Johnson Pharmaceutical Research and Development has proposed that doripenem be approved for treating nosocomial pneumonia, including VAP.

Those voting against approval had concerns about the studies, which included irregularities in the data and excess mortality in patients in one of the two studies among doripenem-treated patients. Several of those voting yes said they were supporting approval with reservations, citing the same reasons.

Doripenem, marketed as Doribax, was approved in October 2007 for treating complicated urinary tract infections and complicated intra-abdominal infections. Doripenem is a carbapenem in the β-lactam class of antibacterial agents that has broad antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria, according to the company.

The data submitted for approval included two phase III, multicenter, randomized, open label, active control studies of adults with clinical, radiologic, and microbiologic evidence of nosocomial pneumonia, conducted by Johnson & Johnson. One study compared doripenem with piperacillin/tazobactam in nonventilated patients with nosocomial pneumonia and those with early-onset VAP (occurring within the first 4 days of hospitalization). The second study compared doripenem to imipenem, another carbapenem antibiotic, in patients with early-onset VAP and late-onset VAP (occurring after 5 or more days of hospitalization).

Both studies were designed to establish "noninferiority" between doripenem and the other treatments, based on the clinical cure rate 6-20 days after treatment was completed. The clinical cure rate was defined as "complete resolution or marked improvement or return to baseline of all signs and symptoms of pneumonia and improvement or lack of progression of all chest x-ray abnormalities, such that no additional antibacterial therapy was required."

In the study of patients with non-VAP and early-onset VAP, the clinical cure rates were 81.3% among those who received doripenem and 79.8% among those who received piperacillin/tazobactam. In the study of patients with early and late-onset VAP, the clinical cure rate was 68.3% among those treated with doripenem, compared with 64.8% of those who received imipenem. Adverse events were similar to those seen with doripenem for other approved indications, and with carbapenems, and "in general, was similar" to the adverse events in patients on the comparator antibiotics, according to the company. ■

C. difficile Hospitalizations, Deaths on the Upswing

BY DIANA MAHONEY
New England Bureau

A sharp rise in the number of adult hospitalizations and deaths attributable to *Clostridium difficile* infection over a 6-year period has investigators calling for increased allocation of public health resources aimed at the prevention of disease caused by the GI pathogen.

In a population-based analysis of adult hospitalizations related to *C. difficile*–associated disease (CDAD) between 2000 and 2005, Dr. Marya D. Zilberberg of the University of Massachusetts School of Public Health and Health Sciences, Amherst, and colleagues determined that the incidence of adult CDAD hospitalizations rose from 5.5 cases per 10,000 population in 2000 to 11.2 per 10,000 population in 2005. Furthermore, the investigators reported that the CDAD-related, age-adjusted case fatality rate rose from 1.2% in 2000 to 2.2% in 2004.

"In our analysis, we detected a 23% annual increase in CDAD hospitalizations in the 6-year period from 2000 through 2005," the investigators wrote. "Moreover, the absolute number of CDAD hospitalizations more than doubled in all age groups except the youngest, for whom they increased by 74.1% over the study period." The rate of increase in the incidence of CDAD was steepest in the group aged 85 years and older, followed by the group aged 65-84 years, the group aged 45-64 years, and the group aged 18-44 years (Emerg. Infect. Dis. 2008;14:929-31).

The numbers help explain the increasing mortality rates related to CDAD, the authors wrote, referring specifically to a recent report documenting a 35% per year increase in the number of CDAD deaths from 1999 through 2004 (Emerg. Infect. Dis. 2007; 13:1417-9). "By observing a 23% per year increase in the volume of hospitalizations with CDAD in the period 2000-2005, we demonstrate that at least half of the reported mortality increase with CDAD is due to an increase in the incidence of hospitalizations with this severe infection," they stated, noting that the increased hospitalization likely represents the effects of increased virulence of the organism as well as growing resistance to some antibiotic treatments.

Data for the current analysis were obtained from the National Inpatient Sample, which is a 20% sample of U.S. community hospitals, weighted to provide national estimates. The investigators identified CDAD by ICD-9-CM code 8.45 for intestinal infection with *C. difficile,* and age-stratified the number of discharges per year.

"The rapid rate of growth of CDAD-related hospitalizations and mortality is alarming, particularly in view of the aging U.S. population," the authors wrote. "If this rate of rise, along with the increase in virulence and diminished susceptibility to antimicrobial drug treatments, persists, *C. difficile*–associated disease will result not only in a considerable strain on the U.S. health care system but also in rising numbers of deaths related to this disease." For this reason, they stressed, "research into the best preventive strategies, such as limiting the use of antimicrobial agents in both human disease and the food supply, is a public health imperative." ■