Starch Solutions Faster, but Ringer's May Be Safer

Patients with severe sepsis or renal disease may have an increased risk of long-term sequelae with HES.

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

BARCELONA — Hydroxyethyl starch solutions can't be recommended for fluid resuscitation in patients with severe sepsis or septic shock, or in those at risk of renal problems, researchers said at the annual congress of the European Society for Intensive Care Medicine.

The starch solutions are associated with higher rates of acute renal failure and increased 90-day mortality in these patients, especially in those who receive more than the highest recommended dosage of 22 mL/kg of body weight, said Dr. Frank Brunkhorst of the Friedrich Schiller University of Jena (Germany).

Dr. Brunkhorst, who also manages the German Sepsis Society, reported the interim results of the Influence of Colloid vs. Crystalloid Volume Resuscitation in Patients with Severe Sepsis and Septic Shock (VISEP) study.

VISEP, a phase III trial, randomized patients to volume replacement with either 10% hydroxyethyl starch (HES) 200/0.5 solution (10% Hemohes) or Ringer's lactate solution.

The study was powered for 1,200 patients, but it was suspended after the first interim analysis of 600 showed trends of increased renal failure and mortality in the HES group, Dr. Brunkhorst said.

All patients in the study had either severe sepsis or septic shock; their mean age was 64 years. The mean Acute Physiology and Chronic Health Evaluation II score was 20, and the mean Simplified Acute Physiology Score (version II) was 53.

Hemodynamic stabilization occurred significantly faster in the HES group. Mortality at 28 days was slightly but not significantly higher in the HES group, compared with the Ringer's lactate group (27% vs. 24%), a trend repeated for 90-day mortality (41% HES vs. 34% Ringer's lactate).

This significantly increased mortality risk in patients who received high doses of HES was observed only after 3 weeks.

There were no significant differences in the Sequential Organ Failure Assessment scores overall.

However, the coagulation and renal subscores were significantly higher in the HES group, Dr. Brunkhorst said. In addition, almost twice as many HES as Ringer's patients needed hemodialysis during their treatment (31% vs. 19%), with a total of 650 days of dialysis in the HES group and 321 days in the Ringer's group.

Acute renal failure rates were also significantly higher in the HES group (35% vs. 23%).

The highest recommended dosage of HES (22 mL/kg) was exceeded in 99 patients. A subanalysis of this group identified an increase in dose-dependent mortality at 90 days: 75% of those who exceeded the dosage and 49% of those who did not died. "This was highly statistically significant," Dr. Brunkhorst said.

No previous study has identified this significantly increased mortality risk in patients who receive high doses of HES, he said—probably because the observation period was too short. "All the other studies had a follow-up of only a few days. This was a phenomenon observed only after 3 weeks," Dr. Brunkhorst said.

In 2003, when the VISEP study began, 10% HES was the lightest molecular weight and most rapidly degrading colloidal fluid replacement solution available, said Dr. Konrad Reinhart, a coinvestigator of the VISEP trial. Since then, lighter solutions have come to market.

However, he said, no studies have demonstrated enough treatment superiority to convince him to use any colloidal solution instead of Ringer's.

There are many case reports of pruritic dermatitis associated with starch deposits in the dermis.

Autopsy reports have also shown starch deposits in kidney and liver that persisted for more than 10 years after HES treatment, said Dr. Reinhart, director of the department of anesthesiology and intensive care medicine at the University Hospital of the Friedrich Schiller University of Jena.

Dr. Reinhart is also not convinced that acute renal failure is the only factor involved in the increased risk of death in HES patients.

"Several case reports have looked at foamy macrophage syndrome in these patients," he said (Ann. Int. Med. 2002; 137:1013-4), adding that his institution has restricted the use of starch solutions. "We have stopped using them in our unit, and I won't use them at all in sepsis patients," Dr. Reinhart said.

"No data have ever demonstrated a beneficial effect [over Ringer's], but a lot have demonstrated harm." ■

FDA Approves Generic Forms of IV Ciprofloxacin

BY ELIZABETH MECHCATIE
Senior Writer

Several generic versions of the intravenous formulation of the widely used fluoroquinolone ciprofloxacin have been approved by the Food and Drug Administration, as part of what the agency says is its effort to make lower-cost generic drugs more widely available.

The generic formulations are versions of the trade formulation of Cipro IV, approved in 1991 and marketed by Bayer Corp. Ciprofloxacin injection is provided in a concentration of 10 mg/mL, and is packaged in 20-mL and 40-mL vials, and in a 120-mL pharmacy bulk package, according to an Aug. 28 FDA statement announcing the approval.

Drug Topics, an online magazine, listed Cipro IV injection as the top-selling drug in its list of the 200 highest-selling brand name drugs in the United States in 2005, according to the statement. The wholesale acquisition cost of the drugs used in hospitals totaled $115,353,072.

Ciprofloxacin injection is approved for treating infections caused by susceptible strains of designated microorganisms for certain infections in adults, including urinary tract infections, lower respiratory tract infections, nosocomial pneumonia, bone and joint infections, complicated intraabdominal infections, skin and skin structure infections, acute sinusitis, and empirical therapy in febrile patients with neutropenia. It is approved for treating complicated UTIs and pyelonephritis due to *Escherichia coli,* in patients aged 1-17 years, but not as a first choice, according to the Cipro IV label. It is also approved to reduce the incidence of inhalational anthrax after exposure to aerosolized *Bacillus anthracis* in adult and pediatric patients.

The approval of these generic versions of ciprofloxacin injection "can bring significant savings to the millions of Americans who have certain bacterial infections that can be treated with ciprofloxacin," Gary J. Buehler, a pharmacist and director of the FDA's Office of Generic Drugs, said in the FDA statement. "These approvals are another example of our agency's efforts to increase access to safe and effective generic alternatives as soon as the law permits," he added.

Other first-time generics approved by the FDA since June include formulations of the nonsteroidal anti-inflammatory drug meloxicam (Mobic), the antidepressant sertraline (Zoloft), and the cholesterol-lowering drug simvastatin (Zocor). ■

Bacterial Vaginosis Drug Therapies Yield Mixed Results in 4-Way Trial

BY SHERRY BOSCHERT
San Francisco Bureau

MONTEREY, CALIF. — Four strategies that have been proposed to improve treatment of bacterial vaginosis produced mixed results, with only an extended course of metronidazole improving cure rates, and that only in the short term, Dr. Jane R. Schwebke reported.

A double-blind study randomized 568 women with bacterial vaginosis (BV) to one of four treatment arms: daily metronidazole for 7 days; metronidazole for 14 days; metronidazole for 7 days plus 1 g azithromycin on days 1 and 3, or metronidazole for 14 days plus azithromycin on days 1 and 3. The metronidazole was given in 750-mg extended-release form.

BV was cured in 63% of patients who took metronidazole for 14 days, compared with 45% of patients who took metronidazole for 7 days.

At a first follow-up visit 7 days after completion of treatment, BV was cured in 63% of patients who took metronidazole for 14 days, compared with 45% of patients who took metronidazole for 7 days.

By a second follow-up 21 days after completing treatment, however, there was no significant difference in cure rates among any groups.

Azithromycin therapy did not seem to make a difference at either time point, Dr. Schwebke and her associates reported in a poster presentation at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

Any benefit from the longer course of metronidazole in the short term was lost in the long term. "We don't know if that's because of relapse of the problem or reinfection," she said in an interview at the meeting.

Some physicians have advocated using 10-14 days of metronidazole to treat recurrent BV, although they lacked supportive data. Others have suggested that the relatively low cure rates of 50%-80% seen when treating BV with metronidazole or clindamycin may be due to resistant organisms that are susceptible to macrolide antibiotics, such as mycoplasmas and *Mobiluncus curtisii,* noted Dr. Schwebke, professor of medicine at the University of Alabama, Birmingham, and her associates.

Patients with a Nugent score at baseline of 5-8 (reflecting less complicated flora) were more likely to be cured than women with Nugent scores of 9-10, the intent-to-treat analysis found.

Other factors that have been shown in previous studies to affect cure rates also proved significant in this study. Consistent condom use, sexual abstinence, and refraining from douching improved chances of curing BV with treatment. ■