FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings

June 24, 2013

U.S. Department of Health & Human Services: Vaccines, Blood & Biologics – *www.fda.gov*

Purpose: FDA has analyzed recent data that indicate an increased risk of (i) mortality and renal injury requiring renal replacement therapy in critically ill adult patients, including patients with sepsis and those admitted to the ICU; and (ii) excess bleeding particularly in patients undergoing open heart surgery in association with cardiopulmonary bypass. Additional caution regarding the use of these products is warranted.reactions observed in clinical trials for all subjects and patients were injection site pain, headache, chills, fatigue, rash and nausea.

Summary of Safety Issues

Hydroxyethyl starch (HES) solutions are used for the treatment of hypovolemia (low blood volume) when plasma volume expansion is desired. Recent data have associated the use of these products with an increased risk of severe adverse events when used in certain patient populations.

On September 6-7, 2012, FDA convened a Public Workshop[1] in collaboration with the National Heart, Lung, and Blood Institute at the National Institutes of Health, the U.S. Army Materiel Command, Department of Defense, and the Office of the Assistant Secretary of Health, Health and Human Services to discuss the risks and benefits of HES solutions. Panelists presented data from randomized controlled trials (RCTs), meta-analyses and observational studies (described in data summary) that showed increased mortality and/or renal injury requiring renal replacement therapy (RRT), i.e, severe renal injury, when HES was used in critically ill adult patients including patients with sepsis and those admitted to intensive care unit (ICU).

FDA has completed the analysis of data from the RCTs, meta-analyses and observational studies indicating increased mortality and renal injury requiring RRT in critically ill adult patients, including patients with sepsis and those admitted to the ICU who are treated with HES solutions. FDA has concluded that HES solutions should not be used in these patient populations, and a Boxed Warning to include the risk of mortality and severe renal injury is warranted. In addition, FDA has reviewed a meta-analysis of studies conducted in patients undergoing open heart surgery in association with cardiopulmonary bypass and has determined that an additional warning about excessive bleeding is needed in the Warnings and Precautions Section of the package insert.

Recommendation for Patients

Patients should be aware of the risks associated with the use of HES solutions and discuss these risks with their healthcare provider

- Be aware that severe kidney damage has been associated with the use of HES solutions.
- Be sure to follow up with your healthcare provider as requested and follow all instructions. Report any unusual symptoms immediately.
- Symptoms of kidney damage can include:
  - change in the frequency, amount, or color of urine
  - blood in the urine
  - difficulty urinating
  - swelling of the legs, ankles, feet, face, or hands
  - unusual weakness or fatigue
  - nausea and vomiting
  - shortness of breath

Recommendation for Health Professionals

- Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU.
- Avoid use in patients with pre-existing renal dysfunction.
- Discontinue use of HES at the first sign of renal injury.
- Need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in all patients.
- Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.
- Discontinue use of HES at the first sign of coagulopathy. ➢

Data Summary

Mortality and renal injury requiring renal replacement therapy (RRT)

Four HES products are currently FDA approved for the treatment and prophylaxis of hypovolemia: HESPAN (6% HES 450/0.7[a] in Sodium Chloride Injection; B. Braun Medical Inc), Hetastarch (6%) in 0.9% Sodium Chloride Injection (generic equivalent to HESPAN; Teva Pharmaceuticals USA), HEXTEND (6% HES 450/0.7 in physiological solution; BioTime Inc), and Voluven (6% HES 130/0.4 in normal saline; Fresenius Kabi USA, LLC).

Data from randomized controlled trials (RCTs), meta-analyses and observational studies show increased mortality and renal injury requiring RRT in critically ill patients, including patients with sepsis and those admitted to the ICU, and treated with HES. The safety of the higher molecular weight (molecular weight: 450 kDa) HES, (HESPAN, Hetastarch (6%) in 0.9% Sodium Chloride Injection and HEXTEND) was assessed in retrospective studies and meta-analyses. Extrapolation of safety from the lower molecular weight HES to higher molecular weight HES is justified because of similarities in chemical structure and mechanism of action. In addition, both higher and lower molecular weight formulations are metabolized by α-amylase into similar smaller fragments until the renal threshold of excretion (45-60 kDa) is reached.[2] This fact implies that there is exposure to smaller molecular weight fragments that are associated with toxicity when higher molecular weight HES is administered.

Renal injury was not evident in a review of 59 RCTs in which HES products were administered in the operating room to adult and pediatric patients who were undergoing surgery and were followed for a short period of time, < 7days.[3] Possible explanations for this observation include low exposure levels; administration to a medically-optimized, comparatively healthy surgery population; follow-up monitoring for a brief period of time; and/or other unknown factor(s).

Based on the totality of the evidence, FDA considers increased mortality and renal injury requiring RRT in critically ill adult patients, including patients with sepsis and those admitted to the ICU, and excess bleeding in patients undergoing open heart surgery in association with cardiopulmonary bypass, to be HES class effects.

Randomized controlled trials, meta-analyses, and observational studies

Increased mortality and/or renal injury requiring RRT in critically ill adult patients including those with sepsis, and those admitted to the ICU have been reported in three double-blind, multicenter RCTs published in 2012 comparing HES with crystalloid solution in which treated patients were monitored for 90 days.

- The 6S study compared 6% HES 130/0.42 with Ringer's acetate for treatment of hypovolemia in a large population (N=804) of severe sepsis patients. Death or dialysis-dependence at 90 days were co-primary endpoints; incidence of RRT was a secondary endpoint. Total volume of trial fluid administered (median) was 1500 mL on Day 1, 1500 mL on Day 2, and 1000 mL on Day 3. Mortality (201/398 vs. 172/400; p=0.03) increased independently of increased RRT (87/398 vs. 65/400; p=0.04) in the HES treatment arm. This well-conducted study demonstrated both increased mortality and serious renal injury at labeled doses of HES, confirming its toxicity.[4]
- The CRYSTMAS study compared 6% HES 130/0.4 with normal saline in a smaller population (N=196) of severe sepsis patients than 6S. Volume of trial fluid needed to achieve hemodynamic stabilization was the primary endpoint; RRT was a secondary endpoint. Total volume of trial fluid administered (median) was 1000 mL on Day 1, and 500 mL/day on Days 2, 3 and 4, respectively. The difference in mortality was in the direction of an increase with Voluven (40/100 vs. 32/96), but did not reach statistical significance (p=0.33). A trend to increased RRT (p=0.06) was reported in the HES treatment arm (21/100 vs. 11/96).[5]
- The CHEST study compared 6% HES 130/0.40 with normal saline in a heterogeneous adult ICU population (N=7000) that included patients with sepsis (N=1937) as well as elective surgery patients and patients with APACHE II score ≥ 25. The primary endpoint was death or dialysis dependency at Day 90. Total volume of trial fluid administered (median) was 1000 mL on Day 0, and 500 mL/day on Day 1, Day 2, and Day 3. The difference in mortality (597/3315 vs. 566/3336) did not reach statistical ➢

significance. HES subjects experienced significantly greater need for RRT (235/3315 vs. 196/3336, p=0.04), but the incidence of RRT in the sepsis subgroup was not reported.[6]

Meta-analyses and observational studies lend additional support to these findings.

- A Cochrane Collaboration meta-analysis of 34 RCTs using different HES products (130/0.4, 200/0.5, 200/0.6, 70/0.5, 200/0.62, and 450/0.7) to treat hypovolemia found that in a subgroup of studies that captured RRT (9 studies, N=1333) or author-defined kidney failure (12 studies, N=1260) as secondary kidney outcomes, a significant increase was observed in HES-treated sepsis patients; this was not observed in HES-treated trauma/surgery patients. The HES used in these studies included 6% HES 130/0.4 (Voluven), 6% HES 130/0.42, 6% HES 200/0.6, and 10% HES 200/0.5.[7]
- Increased mortality and renal injury requiring RRT were reported in four meta-analyses of RCTs in which different HES formulations were used for fluid resuscitation in critically ill adult patients (N=3156 to 10,391), including patients with sepsis, and those admitted to the ICU. The preponderance of these studies used 6% HES 130/0.4-0.042. [8,9,10,11]
- A single-arm, prospective, observational analysis of adults with severe sepsis (N=1046) who received only one type of colloid for hypovolemia over a 6-year study period reported increased RRT in those receiving Voluven (relative risk, 2.01; 95% CI, 1.34 to 3.02; p<0.001) from 2004 to 2006 compared to those receiving crystalloid from 2008 to 2010.[12]
- A retrospective evaluation of cardiac surgical patients (N=563) found that pentastarch (10% HES 200/0.45) was independently associated with acute kidney injury (AKI, prespecified as a 50% rise in serum creatinine within 4 days): 1.08 (1.04 to 1.12; p=0.001). Risk of AKI was dose-dependent, with doses ≥14 mL/kg predicting AKI.[13]
- A retrospective study of trauma patients (N=2225), 22% (N=497) of whom received HES 450/0.7 as part of their fluid resuscitation regimen, reported increased risk of acute kidney injury: with a relative risk 1.73 (1.30 to 2.28); increased mortality: relative risk 1.84 (1.48 to 2.29); and increased risk of death or acute kidney injury: relative risk 1.90 (1.59 to 2.27) in HES patients.[14]

Excess bleeding

In a meta-analysis of 18 RCTs in patients undergoing open heart surgery in association with cardiopulmonary bypass,[15] use of different HES products, irrespective of molecular weight or degree of molar substitution, was associated with increased bleeding. FDA considers excess bleeding a class effect warranting addition of this new safety information to the Warning and Precautions Section of the PI.

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[a]HES nomenclature comprises two numbers separated by a slash: molecular weight in kD and degree of substitution (percent of CH2CH2OH groups per glucose subunit of the polymer).

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