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Hydroxyethyl Starches: Plus Ça Change, plus C'est la Même Chose

To the Editor:

The review by Westphal *et al.*[1] suggesting that hydroxyethyl starch (HES) 130/0.4 is devoid of most of the adverse effects of "older" starches deserves comment. Despite several decades of widespread HES use, proof of clinical benefit such as improved patient outcome is still lacking, whereas evidence for its negative effects on morbidity and mortality in susceptible patients, and at higher doses, is increasing.[2–4] Not 1 of the 140 studies cited in this extensive review nor any previous meta-analysis[5] could demonstrate the superiority of synthetic colloids or HES over crystalloids as a volume replacement.

The adverse effects of starches are strongly related to the cumulative dose.[6–10] Evidence is now emerging that HES 130/0.4, despite showing some altered pharmacokinetic and pharmacodynamic properties, confers similar adverse effects as HES 200/0.5, including kidney dysfunction,* coagulopathy,[11] pruritus,† tissue storage with risk of organ failure.[12] In cardiac surgical patients, HES 130/0.4 impaired clot formation and strength to a similar degree as HES 200/0.5, whereas albumin had no negative effects.[11] In a pig model of liver injury, HES 130/0.4 had a higher immediate volume effect but provoked uncontrolled hemorrhage, resulting in the loss of all animals, whereas six of seven pigs that received Ringer's lactate stopped bleeding.[13] In rats, chronic application of radiolabeled HES 200/0.5 or 130/0.4 led to reduced overall storage of the 130/0.4 solution; however, both HES solutions accumulated in the kidney in similar amounts.[14]

Surprisingly, although the recommended maximum daily dose for HES 130/0.4 is 50 ml/kg, and there is no stated restriction for overall cumulative dose, the median cumulative dose in studies submitted to the Food and Drug Administration for approval of HES 130/0.4† was less than one maximum daily dose. Furthermore, most of these studies were designed to demonstrate noninferiority of HES 130/0.4 in comparison with HES 200/0.5, HES 450/0.7, or gelatins, which all are substances known to have adverse effects on renal function and coagulation.[15] The interpretation of clinical safety of HES 130/0.4 is also limited because the median observation period for all the studies used for its Food and Drug Administration approval was only 2 days and patients with history of heart, kidney, liver, diabetes, or severe infections and coagulation disorders were excluded from these trials. Adverse effects such as renal dysfunction, foamy macrophage syndromes, and itching may appear only later. Indeed, the increased 90-day mortality rate in patients who received higher cumulative doses of HES (136 ml/kg) in the Volume Substitution and Insulin Therapy in Severe Sepsis trial only became apparent between days 21 and 90.[7]

More recently, we have demonstrated that in patients with severe sepsis, even median cumulative doses of only 100 ml/kg HES 130/0.4 and 86 ml/kg gelatin may result in an increased incidence of acute renal failure.[10] Likewise, Ringer's lactate had markedly less negative impact on urine output and kidney damage in a model of isolated perfused kidneys than both HES 200/0.5 and HES 130/0.4, whereas the differences between the two starches was only minor.[16]

Thus, the statement of Westphal *et al.*[1] that 9 clinical trials on renal function demonstrate the "safety of waxy maize-derived HES 130/0.4" is surprising. One of these trials characterized as "important" is a purely observational study, which did not specify HES solutions and reported a cumulative HES dose of less than 15 ml/kg.[17] Moreover, HES recipients at baseline had less exposure to renal replacement therapy (2.2%) than patients not exposed to HES (4.4%, $P < 0.001$), and actual exposure to HES during the intensive care unit stay was associated with an increased requirement for renal replacement therapy (10.6 *vs.* 9.3%; $P = 0.006$), an effect which did not persist in a multivariate analysis of results from a subset of patients. The other eight studies are unsuitable to detect the nephrotoxic effects of HES. One study in volunteers did not use a control fluid, four compared HES 130/0.4 with other, "older" HES solutions or gelatins, which themselves impair renal function. Mean sample size was small (n = 42), mean cumulative dose was only 65.5 ml/kg, and mean duration of trial was 2.6 days. In only three studies, serum creatinine levels were increased at 60 days.

Westphal *et al.* criticize that a subgroup of patients in the Volume Substitution and Insulin Therapy in Severe Sepsis study received more than the allowed maximal daily dose of HES 200/0.5 at least once during the 21-day study period, but they failed to mention that patients who never received more than 22 ml/kg HES/day also demonstrated a significantly higher incidence of renal failure and need for renal replacement therapy compared with patients who received only modified Ringer's lactate.[7] Their suggestion that tight glucose control might have contributed to the adverse effects of starches in this study is an assumption, which is not sup-

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* Hagne C, Schwarz A, Gaspert A, Giambarba C, Keusch G: HAES in septic shock—sword of Damocles? Schweiz Med Forum 2009; 9:304–6. Available at: http://www.medicalforum.ch/pdf/pdf_d/2009/2009-15/2009-15-138.PDF. Accessed November 5, 2009

† FDA: Center for Biologics Evaluation and Research. Product approval information—new drug applications. NDA review memo (mid-cycle). 2007. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/NewDrugApplicationsNDAs/UCM083393.pdf. Accessed November 5, 2009

ported by the available literature on the effects of tight glucose control on renal function. Like HES 130/0.4 now, before the publication of the Volume Substitution and Insulin Therapy in Severe Sepsis study, HES 200/0.5 was hailed as a "modern" HES solution reported to be easily degradable and eliminated by the kidneys[18] and with only minor effects on coagulation.[19] It seems to be a common pattern to advertise each upcoming new HES product as better until adequately designed and powered clinical trials prove the contrary. In the absence of such trials for HES 130/0.4 and other third-generation starches, it is hard to make a legitimate argument for the use of any of them.[2]

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Comment on Reference to Maximum Dose for Starch

To the Editor:

We thank the authors for their important and informative review article "*Hydroxyethyl Starches: Different Products—Different Effects*" published in the July 2009 issue of ANESTHESIOLOGY.[1] However, there is inaccurate information in the column titled "Maximum Daily Dose, ml/kg" in table 1, which we believe should be corrected. Two references are cited for table 1[2,3]; however, neither provide support for all the maximum daily doses listed. It seems that the main reference provided to support these data is a similar table (also table 1) in the September 2005 issue of ANESTHESIOLOGY.[2] This earlier publication does not provide any references for the maximum daily dose column, other than for mentioning that "All statements are given by the manufacturers."

For example, it is a point of fact that hydroxyethyl starch 670/0.75 in 6% balanced solution (Hextend®, Hospira Inc., Lake Forest, IL) has no maximum daily dose promulgated by the manufacturer in the Food and Drug Administration–approved package insert.* Under "Dosage and Administration," there is language regarding what might "typically" be administered ("Doses of more than 1,500 ml per day for the typical 70-kg patient (approximately 20 ml per kg of body weight) are usually not required . . ."), but this is in no way a "maximum

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* http://www.hospira.com/Products/Hextend.aspx. Accessed November 3, 2009.