

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<sup>18</sup> and with only minor effects on coagulation.<sup>19</sup> 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.<sup>2</sup>

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(Accepted for publication November 3, 2009.)

## 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*.<sup>1</sup> 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<sup>2,3</sup>; 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*.<sup>2</sup> 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

Dr. Gan received research support and honoraria from Baxter (Deerfield, Illinois), honoraria from Fresenius-Kabi (Bad Homburg, Germany), and research support from Hospira (Lake Forest, Illinois). Dr. Roche received honoraria from Fresenius-Kabi. Dr. Mythen received honoraria and travel expenses from B Braun (Irvine, California), Baxter, and Fresenius-Kabi.

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

daily dose” or “safe recommended dose” as some have erroneously argued.

For most of the starches, and certainly for hydroxyethyl starch 670/0.75 (Hextend®) and hydroxyethyl starch 600/0.7 (Hespan®, B. Braun Medical Inc., Irvine, CA), it is impossible to designate any safe maximum dose. No dose-finding randomized trials (or observational studies) have ever been done that demonstrate that 20 ml/kg is “safe” but 21 ml/kg causes a clinically significant worse outcome. Observational studies are very confounded in this setting because patients who receive larger volumes of these starches invariably have more extensive surgery and/or bleeding or may require more blood and blood products. Therefore, in the absence of data from well-designed randomized trials, it is impossible to know whether the larger volume of starch is a cause of bleeding or a marker for more complex surgeries with an expected increased blood loss. Multivariate analysis is an imperfect science and cannot control for this level of confounding. *In vitro* studies, which assess the impact of dose *via* increases in percent hemodilution, cannot be used to define a clinical “maximum safe dose.” Finally, it is possible that even if larger doses have theoretical effects on bleeding risk, these effects may be balanced by theoretical benefits of starch related to decreased tissue edema.

In summary, we are not arguing that there is not a provable maximum safe dose for some of these fluids. However, based on existing data, it is impossible at this time to cite a maximum daily dose for some of these fluids, as has been published.<sup>1,2</sup>

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(Accepted for publication November 3, 2009.)

## In Reply:

The intention of our review article was to describe pharmacologically and clinically important differences of hydroxyethyl starch (HES) products.<sup>1</sup> We appreciate the interest in this article and take the opportunity to comment on the points raised in the letters.

In 2007, the Sepsis Occurrence in Acutely Ill Patients study group, with Dr. Reinhart as coauthor, reported that the use of HES had no influence on renal function or the need for renal replacement therapy in critically ill patients.<sup>2</sup> After the publication of the Volume Substitution and Insulin

Therapy in Severe Sepsis trial,<sup>3</sup> which failed its coprimary endpoints, that is, differences in the rate of death at 28 days and the mean score for organ failure, Dr. Reinhart and associates have vigorously argued against the use of HES. They repeatedly and polemically stated that all HES types are the same.<sup>4,5</sup> This claim may reflect flaws in the Volume Substitution and Insulin Therapy in Severe Sepsis study design and considerable protocol violations that accounted for renal dysfunction and death of 26 patients treated with a hyperoncotic pentastarch solution. To date, the authors of the Volume Substitution and Insulin Therapy in Severe Sepsis trial have not provided a pharmacologic justification why HES 200/0.5 (10%), with known accumulation in the plasma and tissue was used, although the more modern and more rapidly metabolizable HES 130/0.4 (6%) was available since 1999. In this context, it is especially noteworthy that acute kidney injury after administration of hyperoncotic colloids had repeatedly been shown before.<sup>6–9</sup>

Although Reinhart *et al.* refer to the importance of cumulative doses of starches, they refrain from quantitative pharmacologic considerations. For example, kidney storage after 52 days in the cited rat model amounted to 0.019% of the given cumulative dose of 12,600 mg/kg, merely reflecting continued renal excretion and amounting to 2.4 mg/kg body weight HES substance in the organ, a small proportion of the total dose given, which can hardly be interpreted as relevant accumulation.<sup>10</sup> Hagne *et al.*<sup>11</sup> describe a case report of a patient who received repetitive HES infusions, although suffering from dialysis-dependent renal failure, which is a well-documented contraindication for HES. In the study cited for coagulopathy,<sup>12</sup> and in another trial,<sup>13</sup> chest tube drainage was not higher after HES 130/0.4 than after albumin (means: 895 *vs.* 990 ml,  $P = 0.98$ ). Data reporting less blood loss and transfusion needs after HES 130/0.4 compared with HES 200/0.5<sup>14–16</sup> have been ignored.

Although pruritus is a known side effect of all HES preparations, it is strongly dependent on dose and storage characteristics.<sup>17,18</sup> Notably, the patient referred to in the case report<sup>19</sup> received a cumulative dose of 1.2 kg of different HES types. The liver trauma animal experiment of Zaar *et al.*<sup>20</sup> is cited and interpreted incorrectly. The HES animals were not lost before the end of the experiment but were followed up longer than Ringer’s lactate animals. Fixed doses of crystalloid *versus* colloid were applied in the early phase, with expectedly stronger hemodilution and higher mean arterial pressures in the colloid group, and with consecutive larger bleeding in the colloid group. In the setting of uncontrolled hemorrhage, however, higher mean arterial pressure values are not necessarily beneficial, even when using crystalloids only.<sup>21</sup> In the isolated kidney model of Hüter *et al.*,<sup>22</sup> the authors reported significant differences of HES 200/0.5 (10%) and HES 130/0.4 (6%), showing a more proinflammatory effect of HES 200/0.5 and less tubular damage for both Ringer’s lactate and HES 130/0.4 (6%) compared with HES 200/0.5 (10%).

The documentation of Food and Drug Administration approval has been cited selectively. In fact, the Food and