Nephrotoxicity of hydroxyethyl starch solution

Editor—Delayed graft function (DGF) after transplantation of cadaver kidneys is associated with poorer subsequent graft survival.¹ Fluid management during the donor operation can significantly modify the risk of DGF. Thus, in a blinded randomized trial of 69 kidney transplants from brain-dead donors,² volume loading with a mean of 2100 ml hydroxyethyl starch (HES) increased the incidence of DGF (P=0.029). In the subset of patients with renal biopsies, osmotic nephrosis-like lesions were observed among all HES recipients, but none of the control group. Such lesions are consistent with HES deposition in renal tissue and have been found to persist as long as 10 yr after HES exposure.³ In a recent study of 262 consecutive brain-dead donors, exposure to >750 ml HES was an independent risk factor for DGF, with an odds ratio (OR) of 1.80 and 95% confidence interval (CI) of 1.11–2.94.⁴ It has been proposed that the molecular weight and substitution of HES solutions might be important determinants of adverse renal effects. For instance, it was suggested that the increased risk of DGF might reflect the particular HES solution used, which was 200 kDa in molecular weight and 0.62 in substitution (HES 200/0.62).⁵ In a new retrospective study of 64 brain-dead donors enrolled over a time period of 8 yr, Blasco and colleagues⁶ hypothesized that HES 130/0.4 might reduce renal dysfunction in transplant recipients. Since case–controls were matched only at the donor patient level, and not the recipient, long-term differences in the recipients are hardly interpretable. More importantly, no difference in incidence of DGF could be detected between the groups receiving HES 130/0.4 and HES 200/0.62 (P=0.27). Similarly, in a prior retrospective study of 109 brain-dead kidney donors, DGF incidence did not differ between donors receiving HES 200/0.5 vs HES 450/0.7 (P=0.42).⁵ Customarily defined as the need for dialysis within the first week, DGF is essentially acute renal failure (ARF) occurring within the specific context of renal transplantation. HES 200/0.62 administration has been shown to be an independent risk factor for ARF in a randomized trial of 129 patients with severe sepsis or septic shock (OR, 2.57; CI, 1.13–5.83).⁷ Once again, it was speculated that the observed poor outcomes might be restricted to HES 200/0.62, but such has not proven to be the case. The newly reported Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) multicentre randomized trial compared HES 200/0.5 with modified Ringer’s lactate for fluid resuscitation in 537 patients with severe sepsis or septic shock.⁸ HES 200/0.5 increased both the incidence of ARF (OR, 1.81; CI, 1.22–2.71) and recourse to renal replacement therapy (OR, 1.95; CI, 1.28–2.98). Additionally, mortality at 90 days was higher (P<0.001) in patients receiving >22 ml kg⁻¹ HES 200/0.5 (58%) for at least 1 day compared with lower doses (31%). It is possible that tissue deposition may have contributed to the unfavourable outcomes among patients with severe sepsis or septic shock. In a study of 12 young adults who died due to sepsis and multi-organ failure after receiving a mean of 258 ml day⁻¹ HES 200/0.5 over a mean of 41 days, quantitation of HES in necropsy specimens showed that the highest measured mean major organ HES tissue concentration was in the kidney (13.7 mg g⁻¹).⁹ The superior renal safety of ‘modern’ HES solutions such as HES 130/0.4 and HES 200/0.5 has been a perennial claim. Such claims do not square with the evidence reviewed above. More broadly, they are not supported by the totality of pertinent evidence. In a systematic review of 92 studies, including 23 randomized clinical trials, renal impairment was demonstrable after usage of HES solutions spanning the full spectrum of molecular weights and substitutions.¹ The lack of convincing evidence for differences in renal safety is also implicit in the HES 130/0.4 Prescribing Information newly approved by the US Food and Drug Administration (www.fda.gov/cber/ndalabel/voluvenLB.pdf; accessed February 28, 2008). According to the Prescribing Information, HES 130/0.4 is contraindicated for patients with renal failure and oliguria or anuria not related to hypovolaemia and for patients undergoing dialysis. Included among the warnings and precautions in the Prescribing Information are the need to adjust HES 130/0.4 dosage in patients with renal impairment and monitor kidney function in all HES 130/0.4 recipients. In any case, the ability of a given HES solution to improve renal safety would need to be demonstrated in well-designed clinical trials.

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Editor—We thank Drs Brunkhorst and Oppert for interesting considerations about this widely debated issue. We agree that the effects of a given HES solution should be carefully evaluated in clinical practice. That
was the goal of our retrospective study which showed that the use of HES 130/0.4 resulted in similar level of DGF, when compared with HES 200/0.6. However, the serum creatinine levels were lower in the group treated with HES 130/0.4 than in the group treated with HES 200/0.6. This result is still valid at 1 yr. Although only the donors were matched, analysis of recipient characteristics did not show significant differences. Of note, this study was not supported by industry. The limitations of the study design are extensively reported in the discussion section. Use of a randomized design is not feasible since in France HES 200/0.6 was withdrawn from the market many years ago. We did not make a conclusion on the superiority of any given HES but on the need to clarify the safety of third generation HES preparations with low degree of substitution in the field of renal transplantation. One can acknowledge that this conclusion was careful. The results of retrospective studies should be better considered because they reflect the real-life conditions. Regarding the literature, it is not so clear that renal function was affected by the use of a low dosage of third generation colloid if the guidelines for its use are carefully respected, that is, contraindication in patients with renal failure, respect of maximal dosages, and limited duration of use. In our opinion, the multicentre randomized trial entitled ‘Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)’ cannot be used in all conditions. First, we did not investigate patients with severe sepsis. Secondly, the renal function of our patients was by definition normal. In VISEP, it seems that 25% of the patients had an initial level of serum creatinine above 180 μmol litre⁻¹. Use of HES in these patients can be deleterious. Thirdly, the characteristics of the colloid that was used in VISEP are close to our ‘retrospective’ control, that is, the HES 200/0.6. As indicated above, this solution has not been available in France for many years. Fourthly, we infused 34 ml h⁻¹ of colloid to our brain-dead patients. With respect to the mean duration of brain death (18 h), our brain-dead patients received approximately 10 ml kg⁻¹ of HES, that is, <612 ml. Just as reminder, the negative effects in VISEP appeared at a dosage >22 ml kg⁻¹ with a mean dosage of 136 ml kg⁻¹, that is, approximately 8 litre of colloids during the stay.

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**Unexpected awakening from anaesthesia after hyperstimulation of the medial thalamus in the rat**

Editor—We would like to attract the attention of anaesthetists and neurophysiologists to a case in which rats unexpectedly and transiently awoke from anaesthesia during a stereotaxic procedure performed as part of an experimental lesional study. In our opinion, this important observation, described below, further contributes to the current knowledge on the functional mechanisms underlying the induction and maintenance of anaesthetic-induced unconsciousness.

The stereotaxic procedure served as the initial intervention for the study into the role of thalamic activity in EEG scalp-recordings and incorporated ibotenic acid...