Comment on infusion solutions containing HES

The European Medicines Agency (EMA) published on 14 June 2013

> Pharmacovigilance Risk Assessment Committee (PRAC) recommends suspending marketing authorisations for infusion solutions containing hydroxyethyl starch.
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> "PRAC has concluded following a review of the available evidence that the benefits of infusion solutions containing hydroxyethyl starch (HES) no longer outweigh their risks and therefore recommended that the marketing authorisations for these medicines be suspended.
> (…)
> The review of infusion solutions containing HES was triggered by the German medicines agency, the Federal Institute for Drugs and Medical Devices (BfArM), following three recent studies (1, 2, 3) that compared HES with other products used for volume replacement called crystalloids in critically ill patients. The studies showed that patients with severe sepsis treated with HES were at a greater risk of kidney injury requiring dialysis. Two of the studies (1, 2) also showed that in patients treated with HES there was a greater risk of mortality."

The "group of external experts" of the European PRAC as well as the German BfArM may not have understood all aspects of the references quoted above. Therefore, a short comment on these publications is given here summarising facts which call the meaningfulness of these studies into question.

VISEP study (1)

- Patients were excluded when creatinine was > 3.6 mg/dl (320 µmol/l), a limit that is 80 % higher than the manufacturers' warnings, i.e. a creatinine value of > 2 mg/dl (177 µmol/l). The negative effects of hydroxyethyl starch and gelatin on renal function in severe sepsis have been described as early as in 2001 in a paper by Schortgen et al.
- An "older" HES preparation with a molecular weight of 200 was used instead of HES 130 which had been available many years before the start of this study.

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- The HES solution used was a hyperoncotic one with a concentration of 10 % instead of 6 %. The advantage of the 10 % solutions is the rapid effect on blood volume restoration as a consequence of taking up an additional 40 % of its volume by draining fluid out of the extravascular (extracellular) space. This should be used only for a short time, otherwise the extracellular space is dehydrated with negative effects on renal function.
  As a logical consequence, Schortgen et al. published their warning concerning any kind of hyperoncotic colloids (hydroxyethyl starch, gelatin, and albumin) in 2008:
  "… harmful effects on renal function and outcome of hyperoncotic colloids may exist, their use should be regarded with caution."
- The tested HES solution was extremely overdosed (60 % higher than recommended): instead of the maximum of 1.5 litres per day (20 ml/kg/d for a patient with 75 kg bw) recommended by the manufacturers, the patients received a median dose of 2.4 litres on the first day, i.e. 50 % of patients got more than 2.4 litres on the first day. In other words, 50 % of the patients – on one day – actually got more than 3.4 litres expressed as isooncotic HES solution (2.4 + 0.4 %): an increase of blood volume by nearly 70 %.
- The tested HES solution was hyperchloraemic, HES in normal saline with sodium and chloride in an amount of 154 mmol/l each. Hyperchloraemia produces an increase in renal vascular resistance, a decrease of the glomerular filtration rate and, therefore, diuresis, and a drop in blood pressure as a result of a decrease in plasma renin activity (Zander 2006). Hyperchloraemia is nowadays considered to be a risk of kidney injury:
  Chowdhury et al. (2012) demonstrated the negative effect of hyperchloraemia on renal blood flow velocity; Shaw et al. (2012) published their warning concerning the use of 0.9 % sodium chloride: "The most concerning findings were the dramatic differences in … renal dysfunction …"; and Yunos et al. (2012) illustrated the daily change from hyperchloraemic to normochloraemic solutions with reduction of acute renal insufficiency (ARI) from 14 % to 8.4 % and renal replacement therapy (RRT) from 10 % to 6.3 %.

Summary VISEP study

The patients were treated with an overdose of hyperchloraemic, hyperoncotic HES solution, i.e. 3 factors with - each alone – constitute a high risk of kidney injury (Zander et al. 2007) and subsequent mortality.

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All these problems can be avoided by using HES in products known as balanced solutions, i.e. plasma adapted, which are isooncotic (COP), isotonic (osmolality) isoionic (Na, K, Ca), isochloraemic (Cl), isohydric (potential base excess) as described before (Zander 2006).

6S study (2)

This is the only study using HES in a balanced solution, but it exhibits major deficits:

- The documentation of fluid resuscitation is extremely incomplete:
  The baseline data for the hemodynamics for Tetraspan (HES) are incomplete,
  e.g. the CVP > 8 or > 12 mmHg is only availabe for 28 - 38 % of patients,
  e.g. the $ScvO_2$ > 70 % data is only available for 33 - 45 % of patients
  e.g. the Hct < 30% / > 30 % data is available for 0 % of patients.
  The same holds true for the volume administration of Tetraspan (HES) which is documented for:
  e.g. only 94 % of patients on day 1,
  e.g. only 72 % of patients on day 2, and
  e.g. only 44 % of patients at day 3.
- Furthermore, the fact that “Trial fluid was used when ICU clinicians judged that volume expansion was needed in the ICU for a maximum of 90 days”, is unacceptable.
- 36 % of patients within the HES group already suffered from acute kidney injury at time of inclusion (table 1: baseline characteristics).
- The mortality of 51 % at 90 days after randomisation is in obvious contradiction with worldwide results.

Summary 6S study

The weakness of this study is its extremely incomplete documentation, especially concerning volume therapy. Additionally, the unacceptable fact that one third of patients already suffered from acute kidney injury at time of inclusion may have contributed to the unbelievably high mortality. Therefore, the meaningfulness of this study is to be called into question.

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CHEST study (3)

A comparison of HES 130 in normal saline vs. normal saline for fluid resuscitation in intensive care with almost 30 % of patients with sepsis is published. In addition to other solutions, the patients were treated with 526 ± 425 ml (!) per day during the first 4 days, in the sense of fluid resuscitation. Renal replacement therapy (RRT) was not significantly different (7 % vs. 5.8 %, p = 0.04) the same holds true for the 90-day mortality (18 % vs. 17 %, p = 0.26).

Summary Chest study

Again, HES in combination with hyperchloraemia has a high risk of kidney injury for critically ill patients, here with no consequences on both RRT and mortality.

General Conclusions

Obviously, two out of three studies (1, 3) disregard the importance of the basal solution containing HES, i.e. normal saline or balanced. The third one (2) has major deficits concerning documentation, baseline characteristics, and a doubtful mortality. Therefore, none of these studies should be used to determine whether or not HES solutions in general are increasing the risk of kidney injury or mortality. This holds true for critically ill patients including patients with sepsis, or burn or trauma injuries, or patients who are undergoing surgery.

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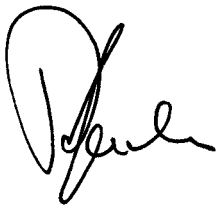

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