



Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin

DGAI Präsident ♦ Direktor der Klinik für Anästhesiologie
Klinikum der Universität München ♦ Marchioninstr. 15
81377 München

European Commission
To His Excellency Mr Vytenis Andriukaitis
EU Commissioner for Health and Food safety
Rue de la Loi / Wetstraat 200
1049 Brussels
Belgium

By email: cab-andriukaitis-webpage@ec.europa.eu

P R Ä S I D E N T

Professor Dr. med. Bernhard Zwißler

Telefon: +49 / 89 / 4400 - 74550
Telefax: +49 / 89 / 4400 - 78885
E-Mail: direktion.anaesthesie@med.lmu.de

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Open letter to the European Commission:

Marketing Authorization of colloid solutions containing hydroxyethyl starch (HES)

Ref: Studies HC-G-H-1504 and HC-G-H-1505 Information on Health Authority Activities for HES Products

Dear Mr. Commissioner,

On behalf 19 European Societies of Anesthesiology*, we would like to express with this open letter our great concern about the current pharmacovigilance procedure for the volume replacement agent hydroxyethyl starch (HES) and ask you to stand up for obtaining marketing authorization from HES. At the same time, we agree with the statements of the Board of Directors of the European Society of Anaesthesiology (ESA) made in their letter from 5th of March 2018.

In 2013, the Referral Procedure concerning the use of hydroxyethyl starch (HES)-containing solutions by the European Medicines Agency (EMA) resulted in changes of the product information such as reduction of the maximum dose (30 ml/kg) and duration of treatment (up to 24 hours) as well as new contraindications including sepsis and critically ill patients. HES is currently indicated for surgical and trauma patients with hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.

Since 2013, all accessible data derived from clinical trials have confirmed the safety and efficacy of HES in these patient populations. International high quality guidelines reflect the

Geschäftsstelle:
Roritzerstraße 27 - 90419 Nürnberg
Telefon: 0911 / 933 78 0 - Telefax: 0911 / 393 81 95
Homepage: www.dgai.de

Prof. Dr. med. Bernhard Zwißler - Präsident
Prof. Dr. med. Alexander Schleppers - Ärztlicher Geschäftsführer
Dipl. Sozialwirt Holger Sorgatz - Geschäftsführer

current knowledge and consider HES equally safe as crystalloids, because there is no sign of increased mortality or renal insufficiency.¹ Therefore, we were very surprised that the EMA initiated an urgent union procedure according to Article 107i and recommended that HES solutions should be completely suspended in 2017. In the explanatory statement, the EMA bases this recommendation on two imposed retrospective drug utilisation studies (DUS) by two pharmaceutical companies that used the same questionnaires. The retrospective and anonymised documentation is based on over 6000 patient charts that did not reveal any adverse safety signal. The DUS showed that the adherence to the new dose and duration been adhered to by almost 100%.

However, hospital physicians apparently documented a high degree of non-adherence to the revised Summary of Product Characteristics (SmPC), especially the use of HES in dehydrated patients. With regard to the fluid status, it is problematic that the main indication for HES (intravascular hypovolemia) was not provided as an option (tick box) in the electronic patient report form (eCRF), but just dehydration and hyperhydration that both represent contraindications. Since most physicians chose the least wrong answer (i.e. dehydration), the results concerning contraindications are artificially inflated. This is further illustrated by the fact that patients may suffer from both dehydration and hypovolemia. If a patient was documented as having received HES and being classified as having had some degree of dehydration during the hospital stay, it does not imply at all that HES was actually infused to treat dehydration. Due to the limited amount of documented data and the imposed design of the study, a validation of the results is not possible and poses more questions than it gives answers.

In addition, it was documented in the DUS that some of the hospitalised patients receiving HES had also sepsis during their hospital stay. However, it is important to note that the DUS only asked, if HES infusion was “timely related to sepsis”. Every clinician knows that sepsis can occur after major abdominal surgery. The exact time point of diagnosis is difficult or practically impossible to be determined in retrospective trials and is certainly independent of the use of HES.

A post-hoc analysis of 460 patients initially included in the DUS in 5 centres with high non-adherence rates revealed that among patients with an initially documented contraindication, only 8 patients actually had one; none suffered from acute sepsis at the time of HES administration. All these aspects were supported and criticised by the independent ad-hoc expert committee appointed by the EMA.² In addition, these experts emphasised that there definitely is a role for HES in the licensed indication and recommended maintaining the marketing authorisation, especially since the benefit/risk balance in perioperative patients is positive.

With consternation we became aware that the PRAC ignored and contradicted every single point not only of their own expert committee, but also statements from international Anaesthesiology Societies and existing well-acknowledged guidelines. The underlying rationale and motivation for such ignorance is not transparent and unacceptable.

Obviously, the EMA followed the opinion of two Sepsis Societies and individual Intensivists. This is especially astounding, as for the patients treated by these specialists there is a clear contraindication which was never challenged in this procedure. Even more incomprehensible is the fact that the discussions about HES are derived from 3 trials performed in critically ill patients.³⁻⁵ VISEP and 6S have been criticised for their methodological shortcomings, contradictive results and large amounts of HES given over

days after initial resuscitation.⁶ Initially, in both trials, critically ill septic patients were nearly all resuscitated with colloids and over 50% of the patients in the respective crystalloid groups received HES at some time. In VISEP, 40% of the HES group received drug overdoses. A recently published prospective observational study in 65 German ICUs showed that duration and amounts of colloids infused in daily practice were dramatically lower than in the two above-mentioned trials.⁷ There were no signs of increased mortality or renal insufficiency caused by colloids in general nor by HES in particular. The third trial is CHEST, which has aroused suspicion to have manipulated their data, as the original protocol, statistical analysis plan and various numbers have been changed since initial publication.⁸ The request for an independent audit and re-analysis of the data proposed by various National Societies, the independent EMA expert committee and international journals (e.g. the BMJ), has been refused by the authors. In the meantime a so called “independent” re-analysis has been published as a letter to the Editor by the original authors, raising more questions than it answers.⁹ To our bafflement, the EMA has not initiated any measures to investigate this critical issue. This is especially surprising, since the principle investigators of these questionable trials are among the strongest advocates for the suspension of the HES marketing authorisation. Their recent open letter to the WHO¹⁰ just shows how desperate they are to protect their data and end all discussions.

In contrast to the above mentioned trials, patients included in the CRISTAL trial were randomised before resuscitation, and the study centers strictly abided to the respective groups.¹¹ In this study, 90-day mortality was significantly improved in the colloid versus the crystalloid group. A subgroup analysis revealed that HES was the only advantageous colloid. This adds to the problem of suspending HES, since alternative colloids are not superior, have a limited availability and are also very expensive (albumin). Gelatin’s safety is sparsely evaluated, and this colloid is characterised by a lower effectiveness. Although Dextrans certainly have the worst benefit/risk ratio among all colloids, they are mentioned as alternative for HES on the EMA website.

In the UK, the yellow card pharmacovigilance system never recorded more than 1 serious adverse event of HES per year with about 100 events for crystalloids. Following the termination of HES sales in 2013, the adverse event rate for crystalloids in the UK has increased by 262%, clearly showing that they are not necessarily a better alternative to HES.

Apart from that, several unmet clinical needs such as plasmapheresis, use in paediatrics (especially cardiac surgery) and prevention of hypotension in patients undergoing caesarean section with spinal anaesthesia remain unattended.

Two major trials in trauma and surgical patients have been requested by the EMA. These already initiated trials are designed to provide answers to open questions and generate further evidence on the safety and efficacy of HES in these important clinical settings. The decision to suspend HES without any signs of harm in these populations and not awaiting the trial results is a politically driven decision that is neither based on clinical, nor on scientific grounds. This is reflected by the fact that a majority of the National Anaesthesiology Societies in Europe does not support the suspension of the HES marketing authorisation, while only 6 out of 36 National Societies, including 3 Non-EU

members, explicitly do so. It is also noteworthy that the PRAC members with divergent opinions expressed in writing that they disagree not only with the recommendation but especially with the procedure and the handling of this case by the EMA. Similarly, the ad-hoc expert group appointed by the EMA published a letter emphasizing that they strongly disagree with the current recommendation and the entire procedure.²

The arguments of the EMA a) that doctors ignore contraindications, b) that it is too difficult to distinguish between patients who might profit or be harmed from HES and c) that further measures would be ineffective, are false and are discrediting physicians all over Europe .

If this procedure is to form a precedent, then from now on, no existing drug might be considered as safe any longer, as any politically active group may trigger a suspension based on the fact that certain patients might experience adverse events, and because an off-label may not always be prevented.

We, the National Societies of Anaesthesiology in Europe*, demand that the EMA pays attention to medical experts and reconsiders their completely unfounded decision. It is time to base the decision on clinical facts and scientific data rather than on political standpoints and questionable data that are hidden and not shared by the investigators despite numerous requests.

Sincerely,



Prof. Dr. B. Zwißler
President

Literature

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Austria Austrian Society of Anaesthesiology, Resuscitation and Intensive Care Medicine

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France Société Française d'Anesthésie et de Réanimation

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