Letter to the Editors

wiener klinische wochenschrift
the middle european journal of medicine
Printed in Austria

Wien Klin Wochenschr (2004) 116/17–18: 640–641

Hydroxyethyl starch – can the safety problems be ignored?

Sirs,

I read Dr. Wiedermann's paper on hydroxyethyl starch (HES) with great interest [1]. The paper is mainly focused on safety issues – the value of HES for stabilizing the hypovolemic critically ill or its beneficial effects on inflammation, organ perfusion and tissue oxygenation are not mentioned. The author has done an excellent job by reviewing a large number of articles on volume replacement and especially on HES. Unfortunately, the overview includes a lot of concerns and problems. The publication is devoid of an appropriate appreciation of the pharmacology of HES products – the statement "HES is like HES" is not supported by the cited papers.

Dr. Wiedermann states that "its (HES 130/0.4) safety profile is less well characterized." This statement is not valid, since numerous published studies in different settings confirmed safety of HES 130/0.4 even in high doses, in patients with renal impairment, in elderly patients as well as in children. No other HES preparation has been studied as extensively in the non-clinical and clinical setting. Unfortunately, he tends to cite "the truth but not the whole truth". Two examples: "Serious cerebrovascular adverse events occurred in 5.7% of the HES 130/0.4 treated patients as compared with 2.8% of the saline control group, although statistically significant differences in adverse events were not demonstrable" [2]. The overall result of the study, namely comparable safety (which was the primary parameter of the study) of high dose HES 130/0.4 and crystalloid and a tendency towards improved outcome after HES 130/0.4 on all neurological scales, was simply ignored. From the study of Grauer et al. [3] (this abstract should not be cited anymore since full publication is available [4]) 15% (n = 3) pruritus patients in the HES group are mentioned, but the 2 pruritus patients in the crystalloid group are omitted.

Regarding anaphylactic reactions, Wiedermann cites data from the systemic review analysis of Barron et al. [5] that are completely contrary to the results published by Laxenaire et al. [6] and Ring and Meßmer [7], who found the lowest rate of anaphylactic reactions with starches (approximately 0.06%) and a very rare incidence of severe anaphylactic reactions (Grade III and IV) during HES administration.

With regard to intravascular persistence, C2/C6 ratio does not take into account that the absolute substitution on C2 is lower for HES 130/0.4/9 compared to HES 200/0.5/5 because of the prevailing influence of molar substitution (MS). It has been shown in several studies that the overall result for HES 130/0.4 compared to HES 200/0.5 is reduced tissue storage and no relevant plasma accumulation, even after repetitive dosing [8–10]. Residual plasma levels after 24 hours, even in severely impaired non-anuric renal dysfunction, were lower then after HES 200/0.5 in healthy volunteers [11, 12].

Dr. Wiedermann's statement that only studies with patients "with absence of critical illness" were performed is not valid (see Neff et al. [13] who included patients with severe head trauma). The reproach that "brain injury patient appear to be at particularly susceptible to the deleterious effects" can definitely be denied by the study from Neff et al. [13].

Most problems arise when the author reviews coagulation and bleeding associated with the use of HES. He cited some papers in which a less degradable HES (HES 200/0.6) was used and not HES 200/0.5 [14]. He is also wrong stating that "data directly comparing HES 130/0.4 and albumin are not available" (see [13]). In the study from Huet et al. [15] statistics (ANOVA) showed a significantly lower blood loss, Langeron et al. [16] showed that use of allogeneic blood was statistically different when using HES 130/0.4 instead of HES 200/0.5. Citing the meta-analysis of Wilkes et al. [17] it is simply not true that higher blood loss for HES 200/0.5 vs. albumin were proven: the 95% confidence interval for the mean difference in bleeding included the value zero, which emphasizes that there were no significant differences between albumin and HES 200/0.5.

Summarizing Dr Wiedemann's overview on HES, it is without doubt that safety problems should never be ignored. The choice of a plasma substitute for treating the hypovolemic patient should be done carefully. The value and possible risks of a certain substance have to be balanced carefully (primum nil nocere). All substances for correcting hypovolemia have their merits and demerits and, unfortunately, the author widely ignores that the alternatives of HES are associated with certain risks. Dr Wiedermann clearly states that none of the available HES solutions, including the newest generation HES 130/0.4, is "risk free". It seems unnecessary to comment on this statement: HES is a drug and to the author's knowledge no drug is free of side-effects. Even natural "substances" such as blood or very widely accepted drugs such as aspirin may have negative or even detrimental side-effects.

The third generation of HES shows favorable physico-chemical characteristics by which several of the disadvantages of the previous generations of HES preparations have been eliminated. An almost uncountable number of HES units have been infused world-wide. Taking into account the millions and millions of units of HES that have been used, the author´s fear of possible side-effects

of the modern HES preparations (e.g. HES 130/0.4) should be relativized! Thus there seems to be no reason why this kind of solutions should be banned from our patients – "excellence is not an act but a habit" (Aristotle).

Joachim Boldt

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