HES 130/0.42 shows less alteration of pharmacokinetics than HES 200/0.5 when dosed repeatedly†

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Background. Hydroxyethyl starches (HES) accumulate in the circulation when administered repeatedly. Accumulation is thought to be partly responsible for undesirable effects (tissue storage, blood coagulation impairment, and itching). HES 130/0.42 with low molecular weight and a low level of substitution has recently been developed in order to reduce those risks.

Methods. In healthy volunteers, the pharmacokinetics of HES 130/0.42/6:1 were investigated using a crossover design with HES 200/0.5 serving as control. Fifty grams of either HES were administered in 4 h day-1 for a period of five consecutive days. HES serum concentrations were used for computation of pharmacokinetic coefficients. Change between the first and fifth infusion in the area under the concentration curve (AUC) served as the primary measurement.

Results. Although the circulation was freed from the load with HES 130/0.42 within 20 h after end of the previous infusion, the amount of HES 200/0.5 increased continuously from one administration to the other. AUC and elimination half-life ($t_{1/2}$) were significantly lower with HES 130/0.42. AUC and $t_{1/2}$ of HES 200/0.5 showed an increase between the first and the fifth administration whereas only a minimal shift was present with HES 130/0.42. Haemodilution via HES 200/0.5 did not change over time.

Conclusions. Repeated administration of HES 130/0.42 shows no accumulation and fewer tendencies to time-dependent changes in pharmacokinetic parameters than HES 200/0.5. The improved reproducibility may improve drug safety, particularly as the accumulation of residual starch with HES 200/0.5 does not contribute to the colloid’s volume effect, but may rather increase the risk of undesired reactions.


Keywords: hydroxyethyl starch, low molecular weight, low substituted; pharmacokinetics, repeated dose; pharmacodynamics; volunteers

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Among the various colloids used for plasma volume replacement, hydroxyethyl starch (HES) is considered to offer a good compromise for both, a volume effect being sufficient by degree and duration to bridge hypovolaemic conditions and to stabilize circulatory function, and a low rate of adverse drug reactions.1 Recently, however,
attention has been drawn to the fact that the terminal elimination of HES from the circulation may take an undesirably long time. Various studies have shown that HES is not completely eliminated from the circulation within 1 day, even after infusion of not more than a single unit of pentastarch (HES 200/0.5), and less so after the administration of either hetastarch (HES 450/0.7) or HES 200/0.62. Under these circumstances, repeated infusions of HES lead to continuously accumulating ‘residual starch’, which appears important for a variety of reasons. First, no method is available in routine clinical practice for the measurement of plasma HES concentrations, with the result that the physician is not able to monitor the actual plasma levels of HES in critical situations. Secondly, it is by no means certain that accumulating HES increases or prolongs the volume effect of the colloid and, finally, there is much concern about the safety aspects of any residual starch fractions in the circulation. Thus, residual HES is considered to be responsible for protracted interaction with components of the coagulation system, and the final metabolic fate of residual HES is uncertain. As the normal mechanisms to degrade and eliminate HES from the plasma are failing when HES is accumulating, other mechanisms must then come into effect, such as the mononuclear phagocyte system or any other system for intracellular uptake and processing of the synthetic colloid. Uptake by tissues and intermediary deposition, however, appear to be related to the pruritic phenomena that have been reported when HES is administered in high cumulative doses.

Under these conditions, it would be of interest for the physician to use HES preparations with reduced tendencies to accumulate. Novel types of HES have recently been developed, with mean molecular weight (M_w) and, more importantly, molar substitution (MS) being lowered compared with the currently available HES blends. The aim of these modifications is to facilitate HES degradation and thereby to minimize the risk of undesirably long retention of HES in the circulation as well as in tissues. This should in turn be associated with a decreased risk of such adverse events (AEs) that depend on the accumulation or storage of HES.

One of these novel low molecular and low substituted preparations is HES 130/0.42/6:1 (i.e. HES with a mean molecular weight of 130 000 Da, an MS of 0.42, and a C2:C6 ratio of 6:1). In the present study, this solution was compared with HES 200/0.5 (middle molecular and middle substituted HES), the current standard HES. The aim of the study was to investigate repeated dose pharmacology and, in particular, to test the hypothesis that the novel HES accumulates less in the circulation than the standard preparation.

**Methods**

**Study design, subjects, and ethics**

The trial was designed as a prospective 2 × 2 crossover, randomized, double-blind study. Nine healthy male volunteers were enrolled into the trial and randomized to the sequence of administration of the study solutions. The volunteers were aged between 27 and 42 and had normal body weight ± 20% (78.6 (4.2) kg [mean (sd)]) per definition by BROCA index [ideal weight = (height – 100) (kg)]. All volunteers had given informed consent in writing before enrolment.

The study was performed in compliance with the Declaration of Helsinki, the regulations of German drug law, and the ICH Guideline on Good Clinical Practice. The study protocol was reviewed and approved by the Ethics Committee of the University Hospital, Frankfurt/Main (Germany). In order to assess safety of the study drugs, the incidence of any AE was documented according to the ICH Guideline on Good Clinical Practice.

**Study solutions**

The investigation solution was a 10% modification of HES 130/0.42/6:1 (marketed as Venofundin™ by B. Braun Melsungen AG, Melsungen, Germany) and the reference solution was standard HES 200/0.5/5:1 (marketed as Infusol™ HES 10% by Serumwerk Bernburg AG, Bernburg, Germany). Blinded administration of the solutions, and food and fluid intake during the treatment days were standardized.

**Protocol**

After an overnight fast, the volunteers were given an infusion of 500 ml of either the investigation or reference solution through an arm vein at a constant rate of 125 ml h⁻¹. Blood samples were collected from the contra-lateral arm vein before, during, and after the infusion in order to measure HES concentration, haemodilution, haemorheology, and various routine serum chemistries. Blood samples were obtained at defined intervals up to 7 h after the end of the infusion. In addition, urine samples were collected to measure urinary HES excretion. The infusions, blood, and urine collections were repeated in the same manner on the next 4 days so that the volunteers completed a 5-day infusion programme with one of the solutions. This was accompanied by a follow-up period of 30 days, during the first 10 days of which the volunteers attended the unit once daily for blood sampling and physical examination. Further blood samples were obtained on the 20th and 30th day after the last infusion. Urinary HES:creatinine ratio was calculated, which allows correct ion for total urine sampling errors. Subsequent to a wash-out of at least 5 weeks’ duration, the first infusion period was followed by a second period with the respective other solution. The study was terminated with a final health examination on the 30th day after the second infusion period.

**Study endpoints**

The primary objective of the study was to investigate if repeated administration of HES 130/0.42 would, by virtue of its different pharmaceutical specification, lead to...
reduced accumulation of residual starch in the circulation compared with 200/0.5.

The pharmacokinetic parameters area under the concentration curve (AUC), maximal concentration (Cmax), total clearance during a dose interval (Cl_tot), and elimination half-life (t1/2) were derived from the serum concentration curve of HES on the respective study days. Colloid osmotic pressure (COP), plasma viscosity, haemoglobin, haematocrit, and α-amylase were measured as pharmacodynamic parameters along with routine chemistries. The time course of haemoglobin concentration was used for the calculation of relative blood volume changes; since blood sampling was standardized during either treatment, no corrections were made for blood sampling losses.

**Laboratory methods**

HES concentrations in serum and urine were determined using the hexokinase/glucose-6-phosphate-dehydrogenase reaction and controlled by the modified anthron method. The limit of detection for the assays of HES 130 and HES 200 in serum is 0.5 mg ml⁻¹. The coefficient of variation was less than 3%. Samples were immediately centrifuged and stored at −18°C for 60 days. Thereafter samples were batch assayed. Measurements of routine laboratory parameters were carried out using standard validated procedures for diagnostic clinical chemistry. Haemoglobin was measured photometrically using the haemoglobincyanide method. The coefficient of variation was less than 2%. Plasma viscosity was measured viscosimetrically (Fresenius Plasmaviscosimeter, Fresenius, Oberursel, Germany). Every day, before starting the measurements, a calibration program was run using the two standard solutions (NP1 and NP2). The range of measurement was 1.1–1.9 mPa. α-Amylase activity was determined enzymatically (Monotest α-amylase PNP; Boehringer Mannheim, Germany). Standard deviation was less than 6%.

**Statistical methods**

Since this was the first study that focused on a possibly reduced cumulative effect of the new HES formulation, it was decided to start with nine volunteers, a customary number in early phase I trials. This number historically had come into use due to the fact that with n = 8, the length of the symmetrical two-sided 95% confidence interval for the difference in means extends just 1 standard deviation in each direction. n = 9 was chosen in the case of a dropout that was not unlikely regarding the long period required to complete the whole study. Due to the fact that this was a 'phase I' trial, no power calculations could be performed.

We hypothesized that the treatment with HES 130/0.42 would result in a lower accumulation than with HES 200/0.5. Accumulation was defined as ΔAUC, that is, the difference between the AUCs of days 5 and 1 (ΔAUC day 5, 0–24h − ΔAUC day 1, 0–24h). AUC was determined by calculating the area under the HES concentration vs time curve for the interval from 0 to 24 h after infusion start, applying the linear trapezoidal rule. With μtest being the expectation of the distribution of ΔAUC of the test drug and μreference the expectation of the distribution of ΔAUC of the reference drug, the study hypothesis could be formulated as: H0: μtest ≥ μreference or H1: μtest < μreference, respectively. Although in the protocol the hypotheses were formulated as one-sided, all statistical analyses were performed in a two-sided way.

For the cumulative effect, that is, the difference of AUC on days 5 and 1, a crossover ANOVA was calculated. As two-factorial ANOVA controlling for infusion day and infusion type for the variables AUC, Cmax, and t1/2, the non-parametric procedure LD-F2 was used (for more detailed information please see: www.ams.med.uni-goettingen.de/). This non-parametric approach based on ranks was chosen since the result does not depend on whether or not a logarithmic transformation is applied to the data, as is common practice in pharmacokinetics. The corresponding macro provided by the authors was run using SAS 9.1.13

For the explorative evaluation of a possible trend over infusion days for haemoglobin concentration, and the corresponding relative blood volume change and COP, plasma viscosity, and α-amylase activity a linear regression per individual and infusion was adapted for the corresponding values at infusion end, thereby indicating whether or not there was a cumulative effect over the successive infusions. For the regression coefficients under each infusion regimen, a sign test was calculated testing the null hypothesis that increases and decreases have the same probability under the respective treatment.

Since this procedure is of low power and with the small number of individuals in this study, a significant result would all the more important.

Additionally a paired t-test for the regression coefficients was calculated comparing the two regimens. All analyses were done using SAS 9.1.13 The (two-sided) level of significance was agreed to be 5%. Graphics were generated using STATISTICA 7.1.14

**Results**

A total of nine subjects completed the trial. Hence, all screened and randomized subjects were included in the pharmacokinetic and safety evaluations. The cumulative dose of HES 130/0.42 infused was 230.4 g (range 217.5–237.2 g) compared with 229.5 g (range 218.6–244.0 g) with HES 200/0.5. Thus, the total dose of both treatments is not different.

The pharmacokinetic parameters revealed marked differences between the two HES preparations. On treatment day 1, serum concentration of HES was lower after the application of HES 130/0.42 and increased less up to day 5 (Fig. 1A) than with HES 200/0.5.
Figure 2A demonstrates the course of AUC\textsubscript{0–24h} values over time. With both preparations, the values calculated from 0 to 24 h, that is, for a single dosing interval, increased from days 1 to 5, however, to different extents. The AUC\textsubscript{0–24h} was 28.41 (6.34) mg ml\textsuperscript{-1} h after administration of HES 130/0.42 on day 1 and increased to 36.57 (8.31) mg ml\textsuperscript{-1} h on day 5. After administration of HES 200/0.5, the AUC\textsubscript{0–24h} was 61.43 (6.99) mg ml\textsuperscript{-1} h on day 1 and hence higher compared with HES 130/0.42. On day 5, an increase in AUC\textsubscript{0–24h} to 88.55 (6.20) mg ml\textsuperscript{-1} h was observed for HES 200/0.5 (P < 0.0001).

Statistical analysis with crossover ANOVA for ln ΔAUC\textsubscript{0–24h} revealed a significant carry-over effect (P < 0.01). The mean difference of HES 130/0.42 with respect to HES 200/0.5 amounted to −1.49 (0.32) demonstrating the slower cumulative effect under HES 130/0.42.

On day 1, the elimination half-life was shorter for HES 130/0.42 compared with HES 200/0.5 [3.81 (0.37) h vs 8.66 (1.02) h]. This difference became greater with increasing duration of treatment and reached values of 4.72 (0.41) vs 17.38 (2.97) h on day 5 (Fig. 2C).

Consistently, lower $C_{\text{max}}$ values were found with HES 130/0.42 compared with HES 200/0.5 as shown in Figure 2 ($P < 0.0001$).

HES recovery rates in urine on each of the five treatment days are shown in Figure 1B.

Figure 1 Time course of HES serum concentration (A) during repeated administration of HES 130/0.42 or HES 200/0.5, respectively, on five consecutive days and cumulative HES recoveries in the urine (B). Healthy volunteers were given daily doses of 50 g HES over 4 h. Urinary HES recovery is expressed as per cent of the cumulative dose of HES from treatment start to the end of the respective treatment day and shows no significant between-group differences.
Fig 2 Change over time of various pharmacokinetic coefficients during repeated administration on five consecutive days of HES 130/0.42 or HES 200/0.5, respectively. (A) Area under the HES concentration curve (AUC$_{0-24h}$) ANOVA LD$_{F2}$: treatment $P < 0.0001$, time $P < 0.0001$, interaction $P < 0.0001$; (B) maximal HES concentration ($C_{max}$) ANOVA LD$_{F2}$: treatment $P < 0.0001$, time $P < 0.0001$, interaction $P = 0.0107$; and (C) elimination half-life ($t_{1/2}$) ANOVA LD$_{F2}$: treatment $P < 0.0001$, time $P < 0.0001$, interaction $P = 0.2338$. Healthy volunteers were given daily doses of 50 g HES over 4 h. With each of the interactions of the coefficients, time and solution effects are significant ($P < 0.0001$; ANOVA).
Within 15 days (5 treatment days and 10 follow-up days), total urinary recovery rates of HES were 54.42 (2.18)% and 58.10 (4.15)% of the total dose of HES 130/0.42 and HES 200/0.5, respectively. There was no difference between the treatment groups.

With both treatments, a decrease in haemoglobin was found on all infusion days (Fig. 3A) (HES 130/0.42: $P < 0.01$; HES 200/0.5: $P < 0.05$). This was most pronounced during the infusion interval and within the first 2 h after each infusion. However, on average, baseline values were not reached within 24 h after infusion start, and this resulted in a slight gradual decline of haemoglobin from the first up to the fifth infusion. The change from baseline persisted until follow-up days 5 and 6 for both treatments. Haematocrit showed a similar time course (data not shown).

There were no significant time or solution effects between the groups with respect to COP and plasma viscosity (Fig. 4A and B).

![Graph](image-url)

**Fig 3** Time profiles of haemoglobin concentration (A) and the corresponding relative blood volume change (B) during repeated administration on five consecutive days of HES 130/0.42 or HES 200/0.5, respectively. Healthy volunteers were given daily doses of 50 g of HES over 4 h. For haemoglobin concentration, overall there are decreases in both groups (HES 130/0.42: $P = 0.0077$; HES 200/0.5: $P = 0.0455$; sign-test for individual regression coefficients); no significant differences, however, exist between the groups ($P = 0.2943$; paired t-test for individual regression coefficients). No significant trends or between-group differences are obvious for change of blood volume.
Fig 4 Time profiles of COP (a), plasma viscosity (b), and α-amylase activity (c) during repeated administration on five consecutive days of HES 130/0.42 or HES 200/0.5, respectively. Healthy volunteers were given daily doses of 50 g HES over 4 h. The overall increase in α-amylase activity is significant with HES 200/0.5 ($P = 0.0077$; sign-test for individual regression coefficients) but not with HES 130/0.42 ($P = 0.7237$). Paired t-test reveals a significant between-group difference ($P < 0.0001$).
The activity of α-amylase increased during the infusions and the first 4 h thereafter. Within 20 h after the infusion, α-amylase activity returned to baseline after treatment with HES 130/0.42, whereas the levels remained elevated with HES 200/0.5 until follow-up day 2. Thereafter, a continuous decline until follow-up day 10 occurred (Fig. 4c). Overall, the course of α-amylase activity corresponded approximately to the concentration of residual starch.

With either treatment, the largest relative change in blood volume became apparent at the end of infusion. The maximal mean increase was found on treatment day 5 to be 11.2% with HES 200/0.5 and 10.8% with HES 130/0.42. Four hundred and twenty minutes after the end of infusion blood volume was similar to pre-infusion values in both treatments (Fig. 3a).

There were no changes in the time course of serum electrolytes (Na⁺, K⁺, Cl⁻, and phosphate) and enzyme activities (creatine kinase, gamma-glutamyl transferase, and transaminases). Blood pressure and heart rate remained within the physiological ranges and no significant changes occurred.

Table 1 shows the frequency distribution of the observed AEs. The most common AE was headache followed by itching with both treatments. Most of the events were classified as of unknown relationship to the administration of the study drugs. All were non-serious and resolved completely. No premature withdrawal due to an AE occurred.

Discussion

The presented data verified that HES 130/0.42 accumulated less in serum than HES 200/0.5. In the blood samples obtained 20 h after the end of the infusion, no accumulation could be detected with HES 130/0.42 on days 1–4, whereas after the fifth infusion, a minimal amount of HES was present. With HES 200/0.5, the colloid’s serum concentration increased from day to day and, after the fifth infusion, had reached a level amounting to as much as one-third of the maximal HES concentration (Cmax) of the first infusion. HES 130/0.42 differs from HES 200/0.5 by two pharmaceutical features, reduced molecular weight and reduced MS. It would appear that the latter is the major cause for the lack of accumulation with HES 130/0.42. A lowering of MS inevitably leads to a proportional increase in unsubstituted anhydroglucose moieties and, more importantly, larger unsubstituted regions within the macromolecule. Thus, those regions are rendered more accessible to enzymatic degradation and cleavage into smaller units is facilitated. It has been demonstrated that the serum half-life of various HES preparations correlates with their MS, whereas the molecular weight shows only weak effects on serum half-life.³ ¹⁵ ¹⁶ Furthermore, in a trial similar to the present one, HES 200/0.5 was compared with HES 200/0.62, a modification with similar molecular weight but considerably enhanced MS. Although lower doses of HES 200/0.62 were administered in this trial than of HES 200/0.5 (30 vs 50 g day⁻¹), plasma concentrations were consistently higher during the 5-day infusion period. Twenty hours after the fifth infusion plasma concentrations of HES 200/0.62 were still higher than the maximal concentrations at the end of infusion on day 1.³ These findings promoted the concept that a further lowering of MS might help to avoid the accumulation of HES almost completely and thereby improve the safety of its use. However, without the development of low substituted HES solutions (Table 2), this aim had been difficult to achieve.

In view of the pharmaceutical and pharmacokinetic features of HES, model independent calculations were chosen in order to assess the pharmacokinetic coefficients of the newly developed HES. In the present trial, HES 130/0.42 showed serum half-lives between 3.81 (0.37) h (day 1) and 4.72 (0.41) h (day 5) and the corresponding values for HES 200/0.5 ranged between 8.66 (1.02) h on day 1 and 17.38 (2.97) on day 5. The increase in all pharmacokinetic coefficients seen with HES 200/0.5 may be because of its propensity to accumulate and to diminish the velocity of elimination (discussed later).

What may be even more relevant than the actual values of the pharmacokinetic coefficients is their change from the first to the last treatment day in the present study. When comparing HES 130/0.42 with HES 200/0.5, the average alteration amounted to 1% vs 13 % with Cmax, 28% vs 44% with AUC0–24 h, and 24% vs 100% with t1/2. Hence, all changes tended to a much larger increase over time with the middle substituted than with the low substituted HES. These alterations over time have to be separated, however, from differences already present after the first treatment day. Whereas the latter are directly due to the different pharmaceutical coefficients of the two preparations (i.e. Mₚ and MS), the changes over time point to the existence of an additional time effect. It would appear that the degradation and elimination processes are becoming increasingly more retarded with HES 200/0.5 than with HES 130/0.42. As either type of HES can clearly be distinguished with regard to
Table 2 Assessment of low substituted HES in the current literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Aim of study</th>
<th>Used solutions</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madjdpour and colleagues&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Molecular weight of HES: is there an effect in blood coagulation and pharmacokinetics?</td>
<td>HES with different molecular weights (130, 500, and 900 kDa) but same molar substitution (0.42)</td>
<td>Molecular weight is not a key factor in compromising blood coagulation. High molecular weight might result in a longer lasting volume effect.</td>
</tr>
<tr>
<td>Woessner and colleagues&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Comparison of clinical effects of a 4-day volume therapy</td>
<td>HES 130/0.4 vs crystalloid solution</td>
<td>HES 130/0.4 or crystalloid solution did not differ regarding safety or haemodynamic efficacy.</td>
</tr>
<tr>
<td>Jungheinrich and colleagues&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Volume efficacy and influence on coagulation</td>
<td>HES 130/0.4 (6%) vs HES 200/0.5; (6%)</td>
<td>Similar with regard to volume efficacy. Coagulation parameters returned more rapidly to normal with HES 130/0.4.</td>
</tr>
<tr>
<td>Leuschner and colleagues&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Tissue storage after repeated i.v. administration to rats</td>
<td>HES 130/0.4 vs HES 200/0.5; &lt;sup&gt;14&lt;/sup&gt;C-labelled</td>
<td>Tissue storage significantly lower. Lower in the total body as well as in the liver and carcass for HES 130/0.4 compared with HES 200/0.5.</td>
</tr>
<tr>
<td>Sander and colleagues&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Equivalence for perioperative volume replacement in major gynaecological surgery</td>
<td>HES 130/0.4 vs HES 200/0.5</td>
<td>Therapeutic equivalence; equally well tolerated and safe.</td>
</tr>
<tr>
<td>Jungheinrich and colleagues&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Pharmacokinetics and tolerability of an i.v. infusion in mid-to-severe renal impairment</td>
<td>HES 130/0.4</td>
<td>Safe administration possible to patients even with severe renal impairment, as long as urine flow is preserved.</td>
</tr>
<tr>
<td>Kasper and colleagues&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Comparison with tolerance and efficacy in patients undergoing preoperative autologous blood donation</td>
<td>HES 130/0.4 vs HES 200/0.5</td>
<td>Proved equivalent in every measured respect.</td>
</tr>
</tbody>
</table>

accumulation of fractions resistant to complete degradation, one may speculate that accumulation *per se* interferes with these processes, for example, through inhibition of enzymatic hydrolysis. This hypothesis is supported by the observation that α-amylase activity increased more and for longer with HES 200/0.5 than with the low substituted HES. The increase of serum α-amylase activity (Fig. 4c) is known to result from the formation of a complex between α-amylase and HES leading to delayed renal elimination of the enzyme. The greater increase and longer persistence with HES 200/0.5 of the complex-bound enzyme appears to be due to the higher plasma concentration and retention of the middle substituted HES when compared with the low substituted preparation. α-Amylase being bound within this complex is likely to be enzymatically less active than the free enzyme or even completely inhibited. Thus, it cannot be ruled out that the binding of α-amylase to HES and the formation of an enzyme–substrate complex *per se* contribute to further inhibition of the degradation process, especially so in the case of HES 200/0.5 with its higher binding of α-amylase to the increased serum HES concentrations.

Overall, the pharmacokinetic behaviour of low substituted compared with middle substituted HES is much more reproducible from day to day as indicated by the less pronounced or almost absent increase in the pharmacokinetic coefficients. The importance of this finding is underlined by the perception that any time-dependent change in pharmacokinetic behaviour would principally be undesirable for a drug. This is not only because of the fact that better reproducibility of serum half-life from day to day ensures a more reliably predictable dose–response relationship, but also safety is favourably improved if no cogitation is needed as to any incalculable increase of serum concentration or prolongation of half-life and persistence of HES in the circulation.

Pharmacodynamic parameters showed alterations known to be associated with the administration of HES in general. Enhanced mean values of COP compared with baseline were obtained mainly 240 min after end of the infusion during all treatment days for either solution. During follow-up, mean COP remained slightly increased up to day 10 (Fig. 4A). Haemoglobin (g dl<sup>−1</sup>) revealed similar decreases after treatment with HES 130/0.42 and HES 200/0.5. These decreases were mainly caused by the dilution effect of the HES infusions (Fig. 3A). However, losses due to blood sampling are likely to have contributed to some degree to the haemoglobin levels reached in the present study. Since blood sampling was standardized with either treatment, any differences regarding its impact on the comparability of the treatments can be ruled out.

The observed differences in the pharmacokinetic coefficients were not reflected in any of the pharmacodynamic parameters with the exception of α-amylase activity (Fig. 4c). In the present study, using repeated dosing administration the changes over time in $C_{\text{max}}$, elimination half-life, and AUC, which were mainly seen with HES.
200/0.5, did not have a similar impact on the pharmacodynamic parameters. In particular, haemoglobin did not decrease with respect to the increase over time in the AUC and the increase in residual starch in the circulation.

As to the safety aspects of our study, mild itching has been observed although not definitely attributed to the HES infusions in one subject and on one occasion with HES 130/0.42 and in two subjects on three occasions with HES 200/0.5. There were a few other unspecific AEs which were probably not related to the administration of the study drugs. Itching has commonly been reported after clinical administration of HES, especially after repeated application. Investigations performed during recent years have revealed that pruritus may develop as a consequence of the accumulation of HES in skin and other tissues. It has been suggested that the incidence of pruritus correlates with cumulative dose and depends on the type of molecular weight of HES administered. In our study, the incidence of pruritus was slightly lower after administration of HES 130/0.42 compared with HES 200/0.5. Due to the small number of subjects (n = 9), however, it is too early to infer clinically relevant differences between the safety profiles of either study drug.

Conclusions

HES 200/0.5 accumulated in the circulation in an amount, which—20 h after the fifth administration—was equivalent to one-third of the maximal concentration after the first administration. There was essentially no accumulation of HES 130/0.42 over the same time. Despite marked accumulation of HES 200/0.5, that is, the much larger amount of colloid being retained in the circulation, its volume effect was not greater than that of HES 130/0.42. The administration of HES 130/0.42 had little impact on the change in pharmacokinetic coefficients over time, whereas treatment with HES 200/0.5 leads to a marked increase in elimination half-life and AUC.

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