Clin Chem Lab Med 2008;46(4):558–562 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.107

Short communication

# Influence of hydroxyethyl starch (6% HES 130/0.4) administration on hematology and clinical chemistry parameters

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## Abstract

**Background**: The chemical inertness of hydroxyethyl starch (HES) might cause interferences of the colloid with a variety of laboratory tests. We aimed to evaluate potential influences of HES 130/0.4, the newest HES type, on several common hematology and clinical chemistry parameters.
**Methods and results**: A convenient sample of 25 patients scheduled for rheological therapy with 500 mL 6% HES 130/0.4 was evaluated. Blood samples were drawn before and after colloid application. Comparing pre- and post-infusion values of a battery of laboratory tests (i.e., hematology and hemostasis parameters, electrolytes, enzymes, kidney and metabolic parameters, lipids, etc.) in time course, a median difference greater than the reference change value for a specific parameter was considered clinically relevant. Among all parameters tested, only serum amylase activity displayed a clinically relevant difference between pre- and post-infusion values (median increase of 85% due to HES administration). By applying in vitro experiments, we demonstrated that serum amylase values obtained in the samples diluted in a 1:1 ratio with HES 130/0.4 and in samples diluted in a 1:1 ratio with 0.9% NaCl displayed a negligible median difference of 3%.
**Conclusions**: The in vivo effect of HES 130/0.4 administration on serum amylase activity observed in our study was pharmacological (real) in nature. With the exception of the influence of HES 130/0.4 on amylase activity, the effects of HES 130/0.4 on other parameters tested in this study can be interpreted as having no clinical relevance.
Clin Chem Lab Med 2008;46:558–62.

**Keywords**: drug effects; hemorheology; hetastarch; plasma substitutes.

Hydroxyethyl starch (HES) solutions are the most common plasma substitutes in Europe and more and more also in other parts of the world (1). The various types of HES differ in degree and position of hydroxyethylation and in average molecular weight (2). Some years ago, a newly designed third-generation HES type, called HES 130/0.4, was introduced into the market (2). HES 130/0.4 has improved elimination properties and optimized influences on the microcirculation compared to older HES types (3–5). As a consequence of the new pharmacological profile, the deterioration of coagulation, a well-known side effect of older HES types, has almost completely disappeared (6–14). Similar to all other HES types, HES 130/0.4 also elevates serum amylase concentration (9, 12). This effect is explained by the generation of HES-amylase complexes impeding the renal excretion of amylase and, thus, inducing accumulation (15, 16). Besides the genuine influence on several laboratory parameters, HES is also able to influence the results of specific measurements (17–23). Although these observations were made for specific HES types only, it is possible that these effects may also occur in other HES preparations.

As the chemical inertness of HES might cause interferences of the colloid with a variety of laboratory tests in vivo and in vitro, we aimed to evaluate potential influences of HES 130/0.4, the newest HES type which is now already in widespread use, on several common hematology and clinical chemistry parameters.

The present single center study was performed prospectively at the St. John of God Hospital Linz, Austria. The study protocol was approved by the Local Ethics Committee in accordance with the Declaration of Helsinki, and written informed consent was obtained from all study participants. To determine possible changes in hematology and clinical chemistry parameters after application of HES 130/0.4, a convenient sample of 25 inpatients of the Department of

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Received July 23, 2007; accepted January 2, 2008

Otorhinolaryngology scheduled for routine application of 500 mL 6% HES 130/0.4 in saline infusion (0.9% NaCl) was evaluated. Furthermore, 15 healthy volunteers (i.e., employees of the St. John of God Hospital Linz) receiving 500 mL saline infusion (0.9% NaCl) served as controls. Exclusion criteria for the study participants were history of HES exposition, volume replacement therapy (e.g., dextrans, gelatins, albumin solutions) or blood transfusions (e.g., erythrocyte concentrates, fresh frozen plasma, platelets) within 2 weeks before enrolment into the present study, and the presence of any comorbidities (with the exception of arterial hypertension and diabetes mellitus).

The aim of the present study was to examine whether the presence of HES 130/0.4 in blood samples affects the results of several common hematology and clinical chemistry parameters. In case of an interference resulting in a ''clinically relevant difference'' between values obtained in a distinct parameter before and after HES 130/0.4 infusion, we additionally aimed to investigate by application of in vitro experiments (in vitro dilution of blood samples by HES 130/0.4 vs. 0.9% NaCl in a 1:1 ratio) whether this effect was masked (false) or pharmacological (real) in nature. The definition of a ''clinically relevant difference'' between values obtained in a distinct parameter before and after HES 130/0.4 infusion was based on the ''reference change'' concept for two successive measurements, as described later in the statistical methods section. The study medication was Voluven® (HES 130/0.4) 6% infusion solution (Fresenius Kabi Austria GmbH, Graz, Austria). The main physiochemical characteristics of Voluven® (HES 130/0.4) 6% infusion solution are as follows: average mean molecular weight of 130 kDa; molar substitution of 0.4; C2/C6 ratio of 9; HES concentration of 6%; initial/distribution half-life ~1.4 h; and terminal/elimination half-life ~12 h (24).

Eligible individuals were asked to participate in the present study, and after appropriate information, they signed the consent forms. The first blood collection was carried out directly before HES 130/0.4 administration (in patients) or saline infusion (in controls). The duration of the infusion was 2–3 h by study design in both patients and controls. Approximately 2 h (range 1–3 h) after the end of the infusion, blood was collected from all study participants for the second time. All hematology and clinical chemistry parameters of interest for the present study (listed in Table 1) were determined from the blood samples obtained before and after the infusion. At each time point, the necessary amount of Vacuette erythrocyte sedimentation rate (ESR) sodium citrate, Vacuette EDTA K3, Vacuette 3.8% sodium citrate and Vacuette serum clot activator tubes (Greiner Bio-One, Kremsmuenster, Austria) were collected. Additionally, each parameter was determined in samples prepared by in vitro dilutions of the blood collected from the patients before HES 130/0.4 administration in a 1:1 ratio with Voluven® (HES 130/0.4) 6% infusion solution and saline infusion solution (0.9% NaCl), respectively.

All laboratory analyses were performed within 2 h after blood collection by commercially available procedures. ESR after 1 h was determined with a Sed Rate Screener 100 (Greiner Bio-One, Kremsmuenster, Austria); white blood cell counts, erythrocyte counts and platelet counts, as well as determinations of hemoglobin and mean cell volume were performed with a Cell-Dyn 4000 system (Abbott Laboratories, Abbott Park, IL, USA); prothrombin time according to Quick, activated partial thromboplastin time, and fibrinogen activity according to Clauss were measured on a BCS coagulation analyzer (Dade Behring, Marburg, Germany) with Dade Behring reagents (Thromborel S, Dade Actin FSL and Multifibren U, respectively); and all clinical chemistry parameters were assessed using serum samples by standardized methods on a COBAS Integra 700 analyzer (Roche Diagnostics, Mannheim, Germany). The following methods were applied: creatinine – kinetic Jaffe reaction without deproteinization (compensated method); blood urea – kinetic test with urease and glutamate dehydrogenase; sodium, potassium and chloride – ion-selective electrodes; calcium – method according to Schwarzenbach with o-cresolphthalein; phosphate – direct phosphomolybdate method according to Daly and Ertingshausen (25); uric acid – enzymatic colorimetric test; bilirubin total – Diazo method; aspartate aminotransferase and alanine aminotransferase – method with pyridoxal-5′-phosphate according to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC); γ-glutamyl transpeptidase – enzymatic colorimetric assay according to the IFCC; alkaline phosphatase – colorimetric assay according to the IFCC; lactate dehydrogenase – optimized standard method according to the German Society of Clinical Chemistry (Deutsche Gesellschaft für Klinische Chemie, DGKC); cholinesterase – method with S-butyrylthiocholine iodide; total creatine kinase (CK) – method according to the IFCC; creatine kinase muscle-brain type activity (CK-MB) – after immunoinhibition with antibodies to the CK-M subunit, the CK-B activity was determined with a method according to the IFCC; α-amylase – enzymatic colorimetric assay according to the IFCC; lipase – enzymatic colorimetric assay with 1,2-O-dilauryl-rac-glycero-3-glutaric acid-(6-methyl-resorufin) ester as substrate; glucose – enzymatic reference method with hexokinase; glycohemoglobin A1c (HbA1c) – total hemoglobin and HbA1c were determined after hemolysis of the anticoagulated blood specimen, total hemoglobin was measured colorimetrically, HbA1c was determined immunoturbidimetrically, the ratio of both concentrations yielded the final percent HbA1c result; total cholesterol – enzymatic colorimetric method; high-density lipoprotein cholesterol and low-density lipoprotein cholesterol – homogeneous enzymatic colorimetric assays; triglycerides – enzymatic colorimetric method with glycerol phosphate oxidase and 4-aminophenazone; C-reactive protein – particle enhanced turbidimetric assay. HES serum concentrations were measured using the hexokinase method as previously described (26).

Statistical analysis was performed with the SPSS software release 13.0 (SPSS Inc., Chicago, IL, USA).

**Table 1** Data obtained from patients and controls before and after HES 130/0.4 administration and saline infusion, respectively, and corresponding reference change values.

| Analytes | Patients receiving intravenous HES (n=25) | | | Controls receiving intravenous NaCl (n=15) | | | RCV |
|---|---|---|---|---|---|---|---|
| | Pre-HES[a] | Post-HES[a] | Difference[c] | Pre-NaCl[b] | Post-NaCl[b] | Difference[c] | |
| ESR, mm | 4 (2–10) | 3 (2–7) | ±0% | 3 (2–8) | 3 (2–7) | ±0% | 37% |
| White blood cells count, $10^9$/L | 7.54 (5.86–8.93) | 7.15 (6.11–9.43) | +1% | 7.31 (5.15–7.86) | 7.22 (6.12–8.74) | +15% | 31% |
| Erythrocytes count, $10^{12}$/L | 4.91 (4.63–5.21) | 4.75 (4.48–4.95) | −4% | 4.84 (4.45–4.93) | 4.74 (4.34–5.03) | ±0% | 9% |
| Hemoglobin, g/L | 149 (141–155) | 141 (135–150) | −4% | 145 (135–150) | 141 (134–154) | ±0% | 8% |
| Mean cell volume, fL | 90.1 (88.0–93.2) | 90.3 (88.0–93.3) | ±0% | 89.7 (88.3–92.3) | 90.1 (88.7–91.9) | ±0% | 4% |
| Platelets, count, g/L | 233 (209–261) | 221 (196–260) | −5% | 236 (211–282) | 241 (220–273) | +2% | 26% |
| Prothrombin time, % | 97 (86–100) | 89 (79–100) | −4% | 100 (100–100) | 100 (98–100) | ±0% | 11% |
| APTT, s | 30.8 (27.5–33.9) | 32.1 (28.6–33.0) | +3% | 29.9 (28.9–30.7) | 30.7 (29.9–31.6) | +3% | 11% |
| Fibrinogen, g/L | 2.66 (2.46–3.31) | 2.43 (2.30–2.96) | −7% | 2.69 (2.33–3.11) | 2.52 (2.12–2.98) | −1% | 30% |
| Creatinine, mg/dL[d] | 1.0 (0.9–1.0) | 1.0 (0.9–1.2) | ±0% | 0.8 (0.7–0.9) | 0.8 (0.7–0.9) | ±0% | 12% |
| Blood urea nitrogen, mg/dL[d] | 14.2 (11.2–17.6) | 12.7 (10.9–16.2) | −7% | 12.8 (10.3–14.9) | 11.4 (8.8–14.1) | −9% | 34% |
| Sodium, mmol/L | 139 (137–139) | 139 (137–140) | ±0% | 139 (137–140) | 139 (138–139) | ±0% | 2% |
| Potassium, mmol/L | 4.19 (3.96–4.38) | 4.00 (3.86–4.16) | −3% | 4.31 (4.22–4.44) | 4.25 (4.14–4.45) | −1% | 13% |
| Chloride, mmol/L | 102 (101–104) | 103 (102–105) | +1% | 103 (103–104) | 103 (102–105) | ±0% | 3% |
| Calcium, mmol/L | 2.37 (2.29–2.52) | 2.33 (2.20–2.42) | −3% | 2.45 (2.35–2.51) | 2.46 (2.34–2.51) | ±0% | 5% |
| Phosphate, mmol/L | 1.2 (1.0–1.2) | 1.0 (0.9–1.2) | −8% | 1.1 (0.9–1.2) | 1.1 (1.0–1.2) | ±0% | 24% |
| Uric acid, mg/dL[d] | 5.3 (4.2–5.9) | 5.0 (4.0–5.8) | −2% | 4.7 (4.0–5.3) | 4.9 (3.8–5.2) | −3% | 24% |
| Bilirubin total, mg/dL[d] | 0.7 (0.6–1.0) | 0.7 (0.6–1.0) | ±0% | 0.6 (0.5–0.8) | 0.7 (0.6–0.8) | ±0% | 71% |
| AST (GOT), U/L | 23 (19–30) | 20 (17–27) | −11% | 22 (18–29) | 21 (17–28) | −4% | 33% |
| ALT (GPT), U/L | 29 (17–41) | 24 (17–37) | −11% | 20 (13–30) | 19 (13–30) | −3% | 67% |
| γ-GT, U/L | 25 (17–49) | 21 (15–43) | −11% | 16 (13–30) | 17 (13–31) | ±0% | 38% |
| AP, U/L | 35 (28–50) | 32 (25–47) | −6% | 51 (50–68) | 57 (46–67) | ±0% | 18% |
| LDH, U/L | 258 (221–314) | 219 (198–243) | −14% | 175 (136–182) | 167 (131–187) | −1% | 24% |
| CHE, kU/L | 9.8 (8.5–11.0) | 8.8 (7.8–10.1) | −10% | 8.5 (6.8–9.5) | 8.5 (6.7–9.4) | −1% | 20% |
| CK, U/L | 85 (67–140) | 77 (60–141) | −13% | 94 (80–221) | 114 (82–197) | +4% | 63% |
| CK-MB, activity, U/L | 15 (12–17) | 12 (10–13) | −17% | 13 (11–15) | 12 (10–15) | ±0% | 55% |
| Amylase, U/L | 54 (45–75) | 96 (92–137) | +85% | 41 (30–72) | 40 (31–69) | ±0% | 24% |
| Lipase, U/L | 26 (21–41) | 31 (25–42) | +19% | 31 (26–35) | 29 (26–37) | ±0% | 64% |
| Glucose, mg/dL[d] | 97 (87–110) | 97 (90–127) | +1% | 82 (73–111) | 85 (76–90) | +5% | 16% |
| HbA1c, % | 5.3 (5.1–5.6) | 5.4 (5.0–5.6) | +2% | 5.4 (5.4–5.9) | 5.5 (5.3–6.0) | +2% | 6% |
| Total cholesterol, mg/dL[d] | 202 (179–223) | 188 (165–202) | −8% | 188 (165–208) | 193 (161–210) | ±0% | 17% |
| HDL-cholesterol, mg/dL[d] | 55 (48–67) | 52 (44–62) | −6% | 66 (49–79) | 67 (50–80) | +2% | 20% |
| LDL-cholesterol, direct, mg/dL[d] | 117 (102–143) | 106 (95–134) | −9% | 100 (84–119) | 100 (79–117) | −3% | 18% |
| Triglycerides, mg/dL[d] | 87 (64–119) | 118 (69–154) | ±0% | 91 (63–99) | 87 (66–134) | +8% | 58% |
| C-reactive protein, mg/L | 1 (0–1) | 1 (0–1) | ±0% | 1 (0–3) | 1 (0–3) | ±0% | 117% |

ALT, alanine aminotransferase; AP, alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CHE, cholinesterase; CK, total creatine kinase; CK-MB, creatine kinase muscle-brain type; ESR, erythrocyte sedimentation rate; γ-GT, γ-glutamyl transpeptidase; GOT, glutamine-oxalacetic transaminase; GPT, glutamate-pyruvate transaminase; HbA1c, glycohemoglobin A1c; HDL, high-density lipoprotein; HES, hydroxyethyl starch; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NaCl, sodium-chloride; RCV, reference change value. [a]Median values (25th–75th percentiles) obtained before and after HES infusion. [b]Median values (25th–75th percentiles) obtained before and after sodium-chloride infusion. [c]Median differences between pre- and post-infusion values (expressed as percent change compared to the pre-infusion values). [d]Conversion factors to SI units: creatinine, mg/dL×88.4=μmol/L; blood urea nitrogen, mg/dL×0.356=mmol/L; uric acid, mg/dL×59.48=μmol/L; bilirubin total, mg/dL×17.1=μmol/L; glucose, mg/dL×0.0555=mmol/L; total cholesterol, HDL-cholesterol and LDL-cholesterol, direct, mg/dL×0.0259=mmol/L; and triglycerides, mg/dL×0.0114=mmol/L.

Data of hematology and clinical chemistry parameters were expressed as median (25th–75th percentiles). In patients with HES 130/0.4 administration and in controls with saline infusion, differences between pre- and post-infusion values were expressed as percent change of the post-infusion values compared with the pre-infusion values (applied for the data depicted in Table 1). According to the ''reference change'' concept for two successive measurements as mentioned previously, a ''clinically relevant difference'' of values obtained in a distinct parameter before and after HES 130/0.4 infusion was evident by definition, if the median percent change of the post-infusion values compared with the pre-infusion values was greater than the reference change value (RCV) for a specific parameter. RCVs for each analyte are shown in Table 1 and were calculated as follows (27): $RCV = z_p \times \sqrt{2} \times \sqrt{(CV_W^2 + CV_A^2)}$, where $z_p$ is probability density function (generally 1.96 at $p = 0.05$ of both side variations), $CV_W$ is within-subject biological variation and $CV_A$ is analytical variation of the test. $CV_W$ data were retrieved from the Westgard database (http://www.westgard.com/biodatabase1.htm, date of access 25 December 2007). Because no $CV_W$ for ESR is listed in this database, we used a previously published value (28). $CV_A$ data were retrieved from the manufacturers' package inserts or product handbooks; in the case of more than one specification for a certain test, we used the lowest value given.

Of the 25 patients (20 male, 5 female; median age 38 years, range 21–56 years) enrolled into the present study, 13 had acute hearing loss, 10 had tinnitus, one had vestibular syndrome and one had peripheral facial palsy. One patient had concomitant arterial hypertension and one had diabetes mellitus. The median duration of the HES 130/0.4 infusion was 2.4 h (range 2.1–2.9 h), and the median time interval between the end of the HES 130/0.4 infusion and the second blood withdrawal was 2.1 h (range 1.3–2.8 h). The median serum HES concentration at the second blood withdrawal was 0.20 g/dL (range 0.14–0.31 g/dL). In the 15 healthy controls (10 male, 5 female; median age 35 years, range 21–52 years), the duration of the saline infusion and the time interval between the end of the saline infusion and the second blood withdrawal also complied with the study protocol.

In Table 1, the pre- and post-infusion values of each study parameter for both the patients and controls, as well as the median difference of the post-infusion values compared with the pre-infusion values and the RCVs are listed. In the patients, a median difference greater than the RCV was observed only for serum amylase. For this parameter, the median results obtained from samples prepared by in vitro dilutions of the blood collected from the patients before HES 130/0.4 administration in a 1:1 ratio with Voluven® (HES 130/0.4) 6% infusion solution and saline infusion solution (0.9% NaCl), respectively, were 27 U/L (interquartile range 23–33) and 27 U/L (interquartile range 23–38) with a median difference between those values (expressed as percent change compared to the NaCl values) of 3%.

The main finding of the present study was that serum amylase activity was the only parameter among a battery of laboratory tests that was influenced in a clinically relevant manner due to the presence of HES 130/0.4 in vivo in the patients evaluated. Amylase activity increased by 85% in the blood samples obtained after intravenous administration of 500 mL Voluven® (HES 130/0.4) 6% infusion solution compared with the blood samples collected before the colloid administration. As expected, in healthy controls receiving 500 mL saline infusion no relevant effect on amylase activity could be observed. Furthermore, by applying in vitro experiments we demonstrated that no relevant effect on serum amylase activity was detectable by the presence of HES 130/0.4 in diluted blood samples. Comparing the values obtained in the samples diluted in a 1:1 ratio with HES 130/0.4 vs. the samples diluted in a 1:1 ratio with 0.9% NaCl (both derived from the 25 patients before the infusion HES 130/0.4), a negligible median difference of 3% was observed for this parameter.

Considering these issues, we conclude that the in vivo effects of HES 130/0.4 administration on amylase activity observed in our study was pharmacological (real) in nature. Our results argue, therefore, against an interference of HES 130/0.4 itself with the analytical procedure of this laboratory test. This conclusion is supported by the in vitro experiment, where only 3% variation was observed after a 1:1 dilution of the specimens with HES, which contrasts with the larger bias recorded ex vivo.

A major limitation, however, regarding the possibility of generalizing our study results is the fact that we used distinct laboratory methods for the present work as described above, and it is thus possible that using other platforms or other analytical procedures might yield other effects. Therefore, the reproduction of our results in other centers or by multicenter studies would argue for their validity.

The 4% decrease of hemoglobin and erythrocytes induced by the infusion of 500 mL 6% HES 130/0.4 indicates a volume expanding effect of approximately 200 mL at the time of the second examination ~4.5 h after starting the colloid application. This is in accordance with the pharmacological properties of HES 130/0.4 which suggest relevant volume efficacy of a 6% solution for some hours also in situations without initial volume deficit (29, 30). Bearing in mind the complex process of volume normalization after hypervolemic infusion (31), the HES serum concentrations obtained after administration of 500 mL Voluven® (HES 130/0.4) 6% infusion solution in our study suggest a residual colloid amount of approximately one-quarter of the infused 30 g at the time point of the second blood collection, thus being consistent with our above described clinical observations. As not all examined parameters can be considered to decrease linearly with plasma volume changes, we arbitrarily compared the values of the first and the second examination without dilution adjustment, which might be considered another limitation of the study. In this context, it is important to emphasize that the

present evaluation was based on the single administration of 500 mL 6% HES 130/0.4 for the purpose of rheological therapy. Hence, the results obtained in this work may not be extrapolated in clinical situations where volume substitution is necessary (i.e., infusion of higher HES doses in intensive care or emergency medicine).

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