Hydroxyethyl Starch in Balanced Electrolyte Solution (Hextend®)—Pharmacokinetic and Pharmacodynamic Profiles in Healthy Volunteers

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Hextend® is a new plasma volume expander containing 6% hydroxyethyl starch (HES) in a physiologically balanced medium of electrolytes, glucose, and lactate (weight average, molecular weight 670 kDa, molar substitution 0.75). This open-label study was designed to investigate the pharmacokinetic and pharmacodynamic profiles of Hextend® in 21 healthy volunteers. We infused Hextend® 10 ml/kg IV over 20 min and determined serum concentrations of HES at selected intervals over a 7-day period. Serum concentration-time curves indicated mixed pharmacokinetic behavior reflecting a two-compartment model in most subjects. The median serum half-life over 7 days was 38.2 h. The balanced formulation of the suspension medium did not seem to affect distribution, metabolism, or excretion of Hextend® when compared with similar HES. Pharmacodynamic analysis demonstrated decreases in some plasma components compatible with the infusion of that volume of fluid and the duration of plasma volume expansion. Other plasma components remained unchanged, reflecting the benefit of a balanced electrolyte solution. Hemodilution was observed for 24–48 h after short-term infusion of Hextend®. Some hemostatic indices showed moderate changes, and serum amylase demonstrated a temporary increase. Our study suggested that Hextend® has pharmacokinetic and pharmacodynamic profiles that are similar to those of other HES.

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Hydroxyethyl starches (HES) are highly effective plasma volume expanders used for the treatment and prevention of hypovolemia or relative hypovolemia, for acute normovolemic hemodilution, or as priming fluids for extracorporeal units. Their administration has been associated with unwanted side effects, such as platelet dysfunction (1), inhibition of coagulation factors (2), excessive intravascular volume (3), pyrexia (4), itching (5), metabolic acidosis (6), and anaphylactic reactions (7). The search for HES of improved composition continues. Hextend® (BioTime, Berkeley, CA) contains 6% hetastarch in a physiologically balanced medium of electrolytes, glucose, and lactate (Table 1). The weight average molecular weight of the polymer units is 670 kDa, with 80% inside the range of 20–2500 kDa. The degree of molar substitution is 0.75. The polymerized D-glucose units are joined primarily by α-1,4 linkages, with occasional α-1,6 branching linkages. Hextend® received approval in the United States for use as a plasma volume expander in March 1999. Clinical studies suggest that it is a safe and effective alternative to other HES and may have a better side-effect profile. A Phase III clinical trial indicated a favorable coagulation response, less bleeding, and fewer blood and blood product requirements in transfused patients in the presence of Hextend® compared with 6% hetastarch in saline (8). In a study in elderly surgical patients, we compared Hextend® plus Hartmann's solution with 6% HES in saline plus saline (9). Two-thirds of patients receiving saline-based fluids developed hyperchloremic metabolic acidosis, whereas none of the Hextend®- or balanced crystalloid-treated patients did. This study describes pharmacokinetic and pharmacodynamic profiles for Hextend® and examines whether the new balanced formulation may have an

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Table 1. Composition of Hextend®

Variable	Value
Hetastarch	60 g/L
Glucose	0.99 g/L
Sodium	143 mmol/L
Chloride	124 mmol/L
Calcium	2.5 mmol/L
Potassium	3 mmol/L
Lactate	28 mmol/L

appreciable influence on these variables when compared with similar HES. Analogies with established HES are drawn so as to define a position for this newly formulated HES.

Methods

After IRB approval, 21 volunteers were recruited to participate in this study. All subjects gave written informed consent. The same weight-adjusted dose of Hextend® was administered, but blood sampling took place at different intervals during the first 24 h of the study for pharmacokinetic modeling of derived data after random allocation to one of three study groups (Table 2). These groups differed only with regard to blood sampling intervals during the first 24 h. Additional blood samples for HES measurement were obtained at 24, 48, 72, and 96 h and on day 7. Chemistry, hematology, and hemostasis measurements were made before Hextend® administration and 5 min; 1, 6, 24, and 48 h; and 7 days afterward. Samples for urinary HES concentration measurement were taken and total volumes recorded in collections made during 0–1, 1–3, 3–6, 6–12, and 12–24 h postinfusion. Twenty-four-hour urine collection was performed on Days 2, 3, 4, and 7.

Subjects were weighed on the morning of the study. A standard dose of Hextend® 10 mL/kg was administered at a rate of 0.5 $mL \cdot kg^{-1} \cdot min^{-1}$, resulting in a standard total infusion time of 20 min. Routine observations, including blood pressure measurements and determinations of pulse rate and respiratory rate, were made at intervals throughout the study period. Pulse oximetry was monitored for the first 2 h of the study.

Colloidal HES (Hextend®) was quantitated in serum and urine samples after their deproteination by using an established zinc hydroxide denaturation step followed by centrifugation. Supernatant centrifugate was assayed with an anthrone-based protocol. The anthrone reaction is specific for monosaccharide structures (e.g., glucose) and their polyglucan equivalents (10). No noncarbohydrates give the characteristic analytical blue-green chromophore detected in the range of 620 nm. Pneumococcal polysaccharides Type I and II; random or branched homo- or heteroglycans; acetylated, propylated, or ethoxylated substituents at residues 2, 3, 6, or a combination of these; and dextrins and dextrans all produce a positive anthrone response. In this study, none of these compounds served as a competitive analytic issue to the presence of Hextend®. Polyvinyl alcohols can confound the anthrone reaction, but they were not known to be present in analytical samples. Sugar alcohols including mannitol, sorbitol, and others are not reactive with anthrone.

Table 2. Timing Schedule for Blood Sampling According to Group Allocation

Timing (min)	Group A	Group B	Group C
1	X		
2		X	
3			X
5	X		
10		X	
15			X
20	X		
30		X	
40			X
60	X		
90		X	
120 (2 h)			X
180 (3 h)	X		
240 (4 h)		X	
360 (6 h)			X
480 (8 h)	X		
720 (12 h)		X	
1080 (18 h)			X
1440 (24 h)	X	X	X
2880 (48 h, 2 days)	X	X	X
4320 (72 h, 3 days)	X	X	X
5760 (96 h, 4 days)	X	X	X
10080 (168 h, 7 days)	X	X	X

Noncompartment methods were used to determine the following kinetic indices: the area under the plasma concentration-time curve calculated to the 24-h concentration, the total area under the curve from time zero to infinity, the elimination rate constant, the half-life ($T_{1/2}$), the volume of distribution (V_D), and the serum clearance. Blood chemistry was measured with a Beckman CX7 system; hematologic results were obtained with a Coulter Model STKS. Factors VIII, IX, XI, and XII and von Willebrand factor antigen (vWFAg) were measured by a one-stage coagulation assay. For analysis of platelet function, a platelet function analyzer (PFA-100™; Dade Behring, Deerfield, IL) was used.

Descriptive statistics, including mean, SD, mode, and, where appropriate, the range of observations, were calculated for quantitative variables. We used paired Student's *t*-tests for the evaluation of changes from baseline in pharmacodynamic data.

Results

All volunteers were healthy male nonsmokers aged 19–45 yr. None had a history of drug allergy, and

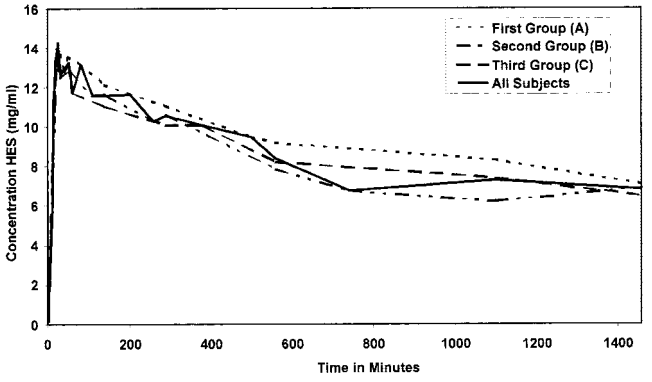

Figure 1. Serum concentration-time curves of hydroxyethyl starch (HES) up to 24 h after the infusion of Hextend® 10 mL/kg over 20 min in healthy volunteers show a rapid initial ascent and faster elimination in the first hours than in the later phase.

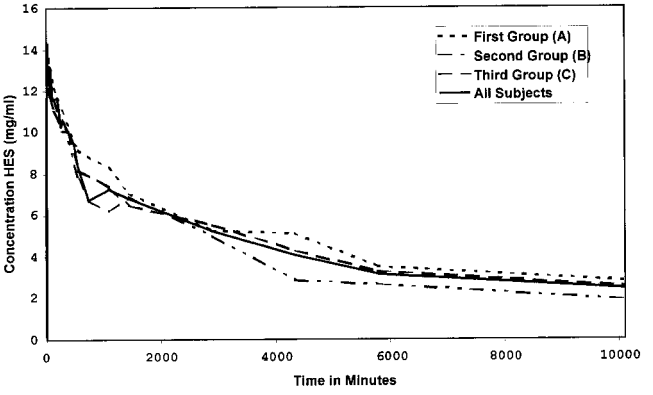

Figure 2. Serum concentration-time curves of hydroxyethyl starch (HES) up to 1 wk after infusion of Hextend® 10 mL/kg over 20 min in healthy volunteers show the progressive decrease in the elimination rate and the presence of HES in the serum after 1 wk.

none took narcotic medications. All had a body mass index of 20–30 kg/m^2, and all were classified as ASA physical status I.

During short-term IV infusion over 20 min, serum concentrations of HES increased rapidly, reaching the peak around the end of infusion. The ascending serum concentration-time curves during infusion for each group (with different sampling times) overlapped, indicating an identical initial distribution during the short-term IV infusion among the three groups. The peak serum concentration had a median of 14.66 mg/mL (range, 8.56 to 20.06 mg/mL). The serum concentration of HES did not reach steady state during the 20-min infusion. Figures 1 and 2 display mean serum HES concentration versus time curves in the first 24 h and the first week.

The serum pharmacokinetic findings are summarized in Table 3. The median VD was 41 mL/kg and was 72 mL/kg corrected for whole blood. The median $T_{1/2}$ of HES within the first 8 h was 4.2 h (range, 1.9–17.7 h), and the median $T_{1/2}$ for the 7-day observation period was 38.2 h (range, 11.0–145.4 h). HES elimination was faster during the first hours after the termination of IV infusion than in the later phase.

Most of the HES administered was eliminated through the kidneys. Consistent with the rapid initial decrement in the serum concentration of HES, the cumulative urine excretion during the first 24 h was 64% of the infused dose. Detectable HES concentrations were observed in urine samples for every subject 1 wk after dosing at 0.20–2.72 mg/mL.

Pharmacodynamic analysis showed hemodilution resulting in decreases in hemoglobin concentration, hematocrit, and red blood cell count lasting for 24 to 48 h. Platelet counts returned to near baseline levels in less than 24 h (Table 4).

The activated partial thromboplastin time, but not prothrombin time, increased during infusion and peaked 6 h after infusion. The thrombin time decreased immediately after Hextend® infusion and remained so for 48 h. Fibrinogen, factor VIII, and vWFAg demonstrated mild to moderate reductions for 48 h. The platelet function analyzer showed moderate and transient increases in closure times (Table 5).

Bilirubin, total protein, alanine aminotransferase, and γ-glutamyl transferase activities exhibited reductions slightly more than expected for that volume infusion alone (Table 6). Albumin, alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase, and creatine phosphokinase showed even greater decreases. In contrast, amylase activity increased at 6 h, reached values four times higher than control at 24 h, and returned to near baseline values after 7 days. Plasma sodium, potassium, calcium, magnesium, chloride, urea, and creatinine remained within their respective reference ranges during and after the infusion of Hextend®.

Discussion

This open-label study was designed to describe the pharmacokinetic and pharmacodynamic profiles of Hextend®. The serum concentration-time curves indicated a mixed pharmacokinetic behavior. The pharmacokinetic profile for most subjects agreed with a two-compartment model. They had a brief distribution phase (a few hours), followed by a long elimination phase (days or weeks). Some subjects' data suggested a single-compartment behavior, with a few others indicating a three-compartment pattern. It is reasonable to derive pharmacokinetic indices by using noncompartment methods with some additional analyses focusing on clinically relevant treatment periods (e.g., the first eight hours).

Because the mean values of most pharmacokinetic variables may be skewed by some outliers, medians are

Table 3. Pharmacokinetic Analysis After Infusion of Hextend® 10 mL/kg

Variable	Mean ± SD	Median (range)
AUC_{0-24} ($mg \cdot h^{-1} \cdot mL^{-1}$)	209.0 ± 11.2	201.8 (129.2–334.4)
$AUC_{0-\infty}$ ($mg \cdot h^{-1} \cdot mL^{-1}$)	926.0 ± 64.3	972.3 (306.1–1386.5)
K_{el} (1 per hour)	0.022 ± 0.003	0.018 (0.005–0.063)
$T_{1/2\ (8\ h)}$ (h)	6.3 ± 1.1	4.2 (1.9–17.7)
$T_{1/2\ (7\ days)}$ (h)	46.4 ± 6.8	38.2 (11.0–145.4)
V_D (mL/kg)	43 ± 5	41 (16–102)
Cl_s (mL/min)	0.98 ± 0.08	0.85 (0.55–2.09)

AUC_{0-24} = area under the plasma concentration-time curve calculated to the 24-h concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from Time 0 to infinity; K_{el} = elimination rate constant; $T_{1/2\ (8\ h)}$ = half-life for the first 8 h; $T_{1/2\ (7\ days)}$ = half-life for the total observation period of 7 days; V_D = volume of distribution; Cl_s = serum clearance.

Table 4. Hematology Results After Infusion of Hextend® 10 mL/kg

Variable	Baseline	5 min	6 h	24 h	48 h
Hemoglobin (g/dL)	14.7 ± 0.9	12.6 ± 1.0	13.4 ± 0.8	14.1 ± 1.0	14.1 ± 0.8
P value		<0.001	<0.001	0.028	0.032
Hematocrit	0.43 ± 0.03	0.37 ± 0.03	0.40 ± 0.02	0.41 ± 0.03	0.42 ± 0.02
P value		<0.001	<0.001	0.036	0.075
RBC ($\times 10^{12}$/L)	4.87 ± 0.34	4.15 ± 0.36	4.45 ± 0.30	4.62 ± 0.32	4.67 ± 0.32
P value		<0.001	<0.001	0.031	0.054
Platelets ($\times 10^9$/L)	213 ± 41	184 ± 40	202 ± 38	205 ± 36	213 ± 37
P value		0.024	0.382	0.516	0.984

Values are mean ± SD. Reference ranges: hemoglobin 13–17 g/dL, hematocrit 0.37–0.50, RBC (red blood cell count) 4.4–5.8 × 10^{12}/L, and platelets 150–400 × 10^9/L. *P* values refer to changes from baseline.

Table 5. Hemostasis Results After Infusion of Hextend® 10 mL/kg

Variable	Baseline	5 min	6 h	24 h	48 h
PT (s)	11.5 ± 1.0	11.9 ± 0.5	11.4 ± 0.5	11.4 ± 0.6	11.4 ± 0.6
P value		0.186	0.740	0.766	0.899
APTT (s)	27.2 ± 2.7	29.3 ± 3.8	30.4 ± 4.1	29.8 ± 4.2	29.3 ± 3.9
P value		0.045	0.006	0.022	0.052
TT (s)	14.8 ± 1.3	11.2 ± 0.9	11.5 ± 0.9	12.0 ± 1.0	12.1 ± 0.9
P value		<0.001	<0.001	<0.001	<0.001
F VIII (IU/L)	1.16 ± 0.25	0.96 ± 0.34	0.73 ± 0.23	0.80 ± 0.20	0.93 ± 0.30
P value		0.030	<0.001	<0.001	0.008
F IX (IU/L)	1.12 ± 0.15	0.93 ± 0.10	0.96 ± 0.11	1.00 ± 0.11	1.04 ± 0.13
P value		<0.001	<0.001	0.005	0.009
F XI (IU/L)	0.97 ± 0.18	0.78 ± 0.11	0.81 ± 0.12	0.86 ± 0.14	0.88 ± 0.13
P value		<0.001	0.003	0.040	0.066
F XII (IU/L)	1.01 ± 0.34	0.84 ± 0.32	0.85 ± 0.29	0.89 ± 0.29	0.91 ± 0.31
P value		0.094	0.114	0.227	0.306
vWFAg (IU/L)	0.90 ± 0.24	0.70 ± 0.29	0.47 ± 0.15	0.50 ± 0.20	0.54 ± 0.19
P value		0.022	<0.001	<0.001	<0.001
Fibrinogen (g/L)	2.04 ± 0.39	1.60 ± 0.30	1.75 ± 0.31	1.89 ± 0.40	1.99 ± 0.46
P value		<0.001	0.015	0.261	0.724
PF $A_{Coll/ADP}$ (s)	91.0 ± 10.1	120.7 ± 23.8	125.4 ± 30.8	90.1 ± 13.4	96.1 ± 15.8
P value		<0.001	<0.001	0.799	0.317
PF $A_{Coll/Epi}$ (s)	130.0 ± 41.9	170.2 ± 53.5	181.8 ± 35.6	145.8 ± 57.1	143.8 ± 41.7
P value		0.016	<0.001	0.322	0.297

Values are mean ± SD. Reference ranges: F VIII, F IX, F XI, F XII, and VWFAg 0.5–1.5 IU/L, fibrinogen 1.5–4.0 g/L, $PFA_{Coll/ADP}$ 71–118 s, and $PFA_{Coll/Epi}$ 94–193 s. PT = prothrombin time; APTT = activated partial thromboplastin time; TT = thrombin time; F = factor; vWFAg = von Willebrand factor antigen. P values refer to changes from baseline.

used in the summary and discussion. Large variations in observed pharmacokinetic indices were expected, because Hextend®, like all HES, is a heterogeneous compound with 80% of its polymer units occurring within the range of 20–2500 kDa. Traditional pharmacokinetic modeling may be applied, but the interpretation of measured or derived variables should take into account the polydisperse nature of HES solutions. The degree of

Table 6. Serum Biochemistry Results After Infusion of Hextend® 10 mL/kg

Variable	Baseline	5 min	6 h	24 h	48 h
Sodium (mmol/L)	138.1 ± 1.7	136.7 ± 1.7	138.8 ± 2.2	138.7 ± 1.8	138.5 ± 1.8
P value		0.015	0.244	0.253	0.420
Potassium (mmol/L)	3.74 ± 0.22	3.83 ± 0.32	3.99 ± 0.34	4.05 ± 0.22	3.98 ± 0.25
P value		0.315	0.008	<0.001	0.002
Calcium (mmol/L)	2.39 ± 0.07	2.25 ± 0.06	2.30 ± 0.06	2.33 ± 0.08	2.36 ± 0.06
P value		<0.001	<0.001	0.007	0.190
Magnesium (mmol/L)	0.79 ± 0.06	0.72 ± 0.06	0.72 ± 0.07	0.76 ± 0.05	0.78 ± 0.06
P value		<0.001	0.001	0.092	0.747
Chloride (mmol/L)	106.2 ± 1.6	106.9 ± 1.4	106.8 ± 1.3	106.4 ± 1.7	106.2 ± 1.5
P value		0.125	0.165	0.707	0.918
Bicarbonate (mmol/L)	25.9 ± 1.4	27.0 ± 1.4	28.1 ± 1.5	27.9 ± 1.7	27.8 ± 1.6
P value		0.022	<0.001	<0.001	<0.001
Urea (mmol/L)	4.9 ± 1.3	4.7 ± 1.3	4.3 ± 1.0	4.4 ± 0.9	5.0 ± 1.3
P value		0.549	0.093	0.484	0.904
Creatinine (μmol/L)	80.9 ± 12.2	81.9 ± 11.9	84.0 ± 16.3	84.0 ± 11.8	84.0 ± 13.4
P value		0.790	0.497	0.416	0.446
Bilirubin (μmol/L)	18.6 ± 6.2	15.3 ± 5.1	15.9 ± 4.6	20.6 ± 7.8	18.9 ± 5.9
P value		0.072	0.199	0.353	0.879
Total protein (g/L)	70.4 ± 3.4	57.5 ± 2.9	61.5 ± 3.5	63.9 ± 4.1	66.1 ± 3.6
P value		<0.001	<0.001	<0.001	<0.001
Albumin (g/L)	43.2 ± 1.8	34.1 ± 1.4	37.8 ± 1.9	39.0 ± 2.7	41.1 ± 2.4
P value		<0.001	<0.001	<0.001	0.002
Glucose (mmol/L)	5.8 ± 0.9	5.8 ± 0.9	5.4 ± 0.8	5.4 ± 0.7	5.3 ± 0.6
P value		0.907	0.174	0.085	0.040
Alkaline phosphatase (IU/L)	62.6 ± 18.5	48.4 ± 14.4	56.1 ± 14.6	54.4 ± 13.9	56.7 ± 15.3
P value		0.008	0.208	0.110	0.262
AST (IU/L)	21.7 ± 7.4	17.3 ± 5.4	18.8 ± 6.5	18.5 ± 6.9	19.2 ± 6.9
P value		0.034	0.192	0.161	0.267
ALT (IU/L)	16.8 ± 9.4	14.0 ± 8.2	15.6 ± 9.8	16.0 ± 11.3	17.0 ± 11.2
P value		0.316	0.691	0.814	0.953
CPK (IU/L)	163.7 ± 156.1	124.7 ± 117.1	128.8 ± 117.7	97.4 ± 66.7	113.7 ± 65.0
P value		0.365	0.419	0.081	0.183
γ-GT (IU/L)	24.0 ± 9.8	19.6 ± 7.7	21.0 ± 8.5	22.1 ± 9.0	22.0 ± 8.4
P value		0.116	0.305	0.526	0.494
LDH (IU/L)	376.5 ± 58.8	284.2 ± 44.7	309.9 ± 42.4	292.9 ± 46.3	313.7 ± 49.3
P value		<0.001	<0.001	<0.001	<0.001
Amylase (IU/L)	55.5 ± 24.1	52.2 ± 22.6	144.5 ± 47.3	212.7 ± 85.0	195.3 ± 69.2
P value		0.658	<0.001	<0.001	<0.001

Values are mean ± SD.

Reference ranges: sodium 135–145 mmol/L, potassium 3.6–5.0 mmol/L, calcium 2.2–2.6 mmol/L, magnesium 0.7–1.0 mmol/L, chloride 98–111 mmol/L, bicarbonate 18–31 mmol/L, urea 2.9–7.0 mmol/L, creatinine 60–125 μmol/L, bilirubin 2.0–20 μmol/L, total protein 60–80 g/L, albumin 32–50 g/L, glucose 3.5–7.9 mmol/L, alkaline phosphatase 30–95 IU/L, aspartate transaminase (AST) 10–35 IU/L, alanine transaminase (ALT) 8–45 IU/L, creatinine phosphokinase (CPK) 33–186 IU/L, γ-glutamyl transferase (γ-GT) 5–50 IU/L, lactate dehydrogenase (LDH) 266–500 IU/L, and amylase 25–125 IU/L. *P* values refer to changes from baseline.

substitution with hydroxyethyl groups, the sites of those substitutions, and the molecular size determine the pharmacokinetic characteristics of the compound. HES fractions below the renal threshold are rapidly eliminated, whereas larger fractions are either broken down by amylase and then excreted mainly through the kidneys or taken up by body tissues and stored in the reticuloendothelial system before being metabolized and excreted (11).

Serum levels of HES did not reach steady state during the short infusion. Peak serum concentrations were observed approximately at the end of IV infusion. Immediately after the infusion, serum HES concentrations decreased rapidly compared with the later phase, resulting in a $T_{1/2}$ of 4.2 hours within the first 8 hours. This time frame of eight hours represents the clinically relevant period after the administration of a single dose of HES. The overall $T_{1/2}$ of 38.2 hours for the 7-day observation period describes the actual fate of the compound.

For HES solutions, the biological $T_{1/2}$ changes as a function of the period of elimination studied (11–13). These unique properties are related to the fact that some degradation-resistant molecule populations remain in the plasma longer than their more vulnerable counterparts. As a result, their $T_{1/2}$ values seem to increase with time. $T_{1/2}$ values ranging from 9 hours to 48 days have been reported for HES, but narrower ranges can be calculated if the period of elimination is specified (12,14).

The corrected median VD of 72 mL/kg was equivalent to the estimated circulating blood volume, indicating that Hextend® was mainly confined to the intravascular space. The median serum clearance was

only 0.98 mL/min. Small levels of HES were detected in both serum and urine samples collected 7 days postdose for every study participant. In our study, 64% of the administered dose of Hextend® was eliminated by the kidneys in the first 24 hours, compared with 40%–46% of the administered dose of HES in two similar studies (15,16). In healthy patients, the potential for accumulation after repeat doses is small (16). It has been suggested that the administration of HES to kidney donors may impair renal function in transplant recipients (17), but one study showed no differences in sensitive markers of renal function after HES administration (18). In our study, none of the indices of renal function demonstrated statistically significant or clinically relevant changes.

Further pharmacodynamic analysis showed that the infusion of Hextend® 10 mL/kg produced decreases in some plasma components consistent with the infusion of that volume of fluid. The duration of these changes mirrored the persistence of plasma volume expansion. Hemodilution was observed for 24–48 hours after the infusion of Hextend® and was consistent with the $T_{1/2}$ of 38.2 hours for the 7-day observation period. Other plasma components, such as plasma chloride, sodium, potassium, calcium, and magnesium, remained virtually unchanged throughout the study period, reflecting the benefit of a balanced electrolyte formulation (19). The increase in plasma bicarbonate is notable and may support suggestions that the administration of Hextend® avoids the risk of producing an iatrogenic metabolic acidosis (9).

Effects of HES on fibrinogen, factor VIII, and vWFAg as a result of binding of coagulation factors to colloid macromolecules have been described (1,2,20), although the administration of clinical volumes seems not to be associated with significant hemostatic defects or hemorrhage (21,22). In this study, Hextend® showed only moderate increases in the activated partial thromboplastin time, whereas the prothrombin time remained unchanged. The shortening of the thrombin time is consistent with previous observations after the administration of HES (23). Changes in platelet function were of a similar magnitude compared with a study of patients who received 10 mL/kg of HES with a molecular weight of 200 kDa (24).

Whereas other enzymes remained unchanged or decreased, a fourfold increase in serum amylase was observed. The infusion of HES stimulates amylase activity in serum, because it is the main enzyme responsible for the elimination of hetastarch (13,15). Hulse and Yacobi (11) suggested that unchanged lipase activity indicated that HES did not affect pancreatic function.

The inhibition of endothelial activation and prevention of neutrophil adhesion during sepsis syndrome may be a benefit of the intravascular presence of HES (25,26). The mechanism seems to be related to a reduced interaction between endothelium and activated white cells in the presence of medium-molecular-weight starch molecules. In an animal model, Hextend® decreased multiple organ failure and xanthine oxidase release after hepatoenteric ischemia-reperfusion (27).

Hextend® is the first colloidal plasma volume expander suspended in a physiologically balanced medium of electrolytes, glucose, and lactate. The pharmacokinetic data suggest that the new balanced electrolyte formulation does not change the distribution, metabolism, or excretion of HES from that expected from the structure and composition of the starch. The pharmacodynamic data confirm that Hextend® infusion results in expansion of plasma volume that decreases over the following 24 to 48 hours. Most biochemical indices remain stable after the infusion of Hextend®, demonstrating the benefits of the balanced formulation of the suspension medium. This may give Hextend® a position where plasma volume expansion is required and biochemical stability is desirable.

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