J Anesth (2012) 26:851–857
DOI 10.1007/s00540-012-1430-6

ORIGINAL ARTICLE

Pharmacokinetics and safety of 6 % hydroxyethyl starch 130/0.4 in healthy male volunteers of Japanese ethnicity after single infusion of 500 ml solution

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Received: 24 February 2012 / Accepted: 30 May 2012 / Published online: 23 June 2012

Abstract
Purpose This phase I study was performed in volunteers of Japanese ethnicity to compare pharmacokinetic data after infusion of 6 % hydroxyethyl starch (HES) 130/0.4 with historical data of Caucasians.
Methods In an open-label, uncontrolled, single-center study, 12 healthy male Japanese volunteers received single intravenous infusions of 500 ml 6 % HES 130/0.4 (Voluven 6 %; Fresenius Kabi Deutschland, Bad Homburg, Germany) over 30 min.
Results Plasma concentration of 6 % HES 130/0.4 was highest at end of infusion (5.53 ± 0.55 mg/ml) and decreased following a biphasic manner. Total plasma clearance and rapid and slow elimination half-lives obtained by a two-compartment model were 1.14 ± 0.16 l/h, 1.12 ± 0.26 h, and 9.98 ± 2.38 h, respectively, and the volume of distribution was 4.76 ± 0.64 l. Mean area under the concentration–time curve was 26.7 ± 3.75 mg/ml h. The total amount of HES excreted into urine was 59.4 % of the applied dose. Hemodilution was observed in all 12 subjects as indicated by a decrease of hemoglobin from 15.5 ± 0.4 g/dl at baseline to 13.8 ± 0.4 g/dl after the end of infusion. Adverse events in this study refer to changes of laboratory parameters and were assessed as not clinically relevant.
Conclusion Single administration of a 500 ml solution of 6 % HES 130/0.4 was confirmed to be safe and tolerable in healthy male Japanese subjects. A rapid renal excretion was observed within 24 h after drug administration, accounting for 96 % of the total amount excreted. A comparison with pharmacokinetic data derived from Caucasians did not reveal significant differences to Japanese and confirmed the good tolerability in both ethnic groups.

Keywords Hydroxyethyl starch · 6 % HES 130/0.4 · Pharmacokinetics · Safety · Japanese healthy male volunteers

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Introduction

Hydroxyethyl starch (HES) solutions are used in most parts of the world to maintain circulating blood volume (normovolemia) or to treat hypovolemia according to the individual need of the patient in various medical applications. Typical applications are all types of surgeries, trauma, burns, and infections, e.g., sepsis. The latest development of HESs is a tetrastarch, i.e., 6 % HES 130/0.4 (Voluven). This product was launched in Germany in 1999 and is available in many other countries worldwide, including the United States, except Japan. The 6 % HES 130/0.4 specification has an average molecular weight (MW) of 130,000 ± 20,000 Da, a molar substitution of 0.38–0.45, and a C2/C6 ratio of approximately 9:1; it has the narrowest molecular distribution of all HES specifications commercially available. Six

percent HES 130/0.4 does not significantly accumulate in plasma and does not show a negative influence on either hemostasis or microcirculation [1–3] compared to other HES preparations. Furthermore, the excellent degradability of 6 % HES 130/0.4 causes no measurable reduction of clinical efficacy, as proven by a comparison of 6 % HES 130/0.4 and 6 % HES 200/0.5 or 6 % HES 130/0.4 and 6 % HES 450/0.7 [4, 5]. Thus, the more rapid elimination of Voluven led to an improved safety profile [6] while plasma volume expansion could be preserved [7]; this is reflected by a maximum daily dose of 50 ml Voluven/kg/day over several days.

As HES products in different preparations have been used in almost all countries throughout the world for 30 years or more, it is thought that no ethnic differences are apparent in their clinical use, and also such are not expected in a phase I study. Therefore, it was decided to perform a phase I study in Japanese volunteers with intravenous administration of 6 % HES 130/0.4 to verify the comparability of different ethnic populations. In accordance with a previous phase I study in Germany [8], 12 healthy male volunteers of Japanese ethnicity received 500 ml 6 % HES 130/0.4 over 30 min intravenously to evaluate the pharmacokinetic and safety data of 6 % HES 130/0.4.

Materials and methods

Study design

After ethics committee approval, 16 healthy male Japanese volunteers aged between 20 and 40 years provided signed informed consent and were enrolled into this open-label, uncontrolled, single-center phase I study. All procedures were performed in accordance with Good Clinical Practice, Pharmaceutical Affairs Law, and other relevant local regulations. Subjects were included whose body mass index was between 18.5 and 25 kg/m^2 and who had a body weight of 55–80 kg. Twelve subjects received study medication and 4 subjects were hospitalized as reserve subjects. In case a subject's health deteriorated between screening and hospitalization examination, he was to be replaced by a reserve subject. Subjects were screened within a period of 1 month before the start of the study, and screening examinations were actually performed within 6–8 days before administration of study drug (6 % HES 130/0.4). Subjects were confined in the Kouryokai CPC Clinic in Kagoshima from the afternoon of the day before study drug administration until 72 h after the start of administration of 500 ml 6 % HES 130/0.4 intravenously over 30 min. Subjects received 500 ml 6 % HES 130/0.4 in 0.9 % sodium chloride solution. Adverse events were assessed until 14 days after the end of study drug infusion.

Dietary restrictions

On the evening preceding the 6 % HES 130/0.4 infusion, subjects were required to drink 1 l water (including water/fluid content of the supplied meal). Approximately 1 h before 6 % HES 130/0.4 administration, a standardized breakfast containing 400 ml water was served. Apart from that, no food intake was allowed within 10 h before the infusion until 3.5 h after start of the infusion, when a standardized lunch was served. No oral intake of fluids was allowed from the end of breakfast until 3.5 h after start of infusion. From 3.5 h until 12.5 h after the start of HES administration, the subjects drank 150 ml water/fluid every hour (1.35 l in total). All other meals were served at the usual mealtimes.

Investigations and assessments

Blood samples were drawn from an indwelling venous catheter of the contralateral forearm from 5 min to 7 h after the start of 6 % HES 130/0.4 administration. Blood was sampled at time points 5, 10, 30, 60, and 90 min after start of infusion and at 2, 4, 6, 7, 24, 48, and 72 h after start of infusion. For the blood drawing from 24 to 72 h after the start of 6 % HES 130/0.4 administration, a de novo venous puncture was done. Urine was collected from 0 to 2, 2 to 4, 4 to 6, 6 to 24, 24 to 48, and 48 to 72 h.

HES in plasma and urine samples was precipitated using acetone. After removal of the supernatant, HES precipitate was dissolved and hydrolyzed into glucose with trifluoroacetic acid. After drying and dissolving in buffer solution, the glucose was determined enzymatically with a glucose analyzer. The limit of quantification (LOQ) for HES 130/0.4 concentrations in plasma and urine was given as 0.08 mg/ml with a relative intraday coefficient of variation (CV) of 2.22 %. Because there were quantifiable urine concentrations at baseline, although very close to LOQ, baseline-corrected post-dosing values were calculated for these cases before deriving urinary pharmacokinetic parameters. Resulting negative values were replaced with 'zero.' Measured concentrations of HES 130/0.4 below the LOQ were considered as 'missing.' Determination of molecular weight of HES in plasma and urine samples was performed using a low-angle laser light-scattering procedure and high performance gel permeation chromatography. Hematology parameters were determined at baseline and at time points 5, 10, 15, 30, 60, and 90 min after start of infusion and 2, 4, 6, 7, 24, 48, and 72 h after start of infusion. Coagulation tests were performed 30, 60, and 90 min and 2, 4, 6, 7, 24, and 72 h after start of infusion. Clinical chemistry parameters (including enzyme tests) were evaluated at time points 15, 30, 60, and 90 min and 2, 7, 24, and 72 h after start of infusion. Urinalysis was

performed at baseline and 7, 24, and 72 h after start of infusion.

Area under the concentration–time curve (AUC) and the maximum concentration (C_{max}) were derived from HES 130/0.4 plasma concentrations by model independent approach as well as $AUC_{(0-tn)}$, terminal half-life ($t_{1/2,z}$), total plasma clearance (CL), volume of distribution at steady state (V_{ss}), cumulative amount of drug excreted into urine (A_e), mean MW, bottom and top fractions MW, in plasma and urine. Two-compartmental modeling was applied on individual HES 130/0.4 plasma concentration–time curves, in particular to derive the half-life of the first elimination phase (alpha half-life, $t_{1/2,\alpha}$), half-life of the second elimination phase (beta half-life, $t_{1/2,\beta}$), the half-life for drug elimination from the central compartment ($t_{1/2,c}$), and the volume of distribution of the central compartment (V_c). All pharmacokinetic calculations were performed using the software WinNonLin 5.1 Professional (Pharsight; a Certara Company, Sunnyvale, CA, USA).

Local and systemic tolerability with respect to safety parameters was assessed at all scheduled time points (including baseline) after start of 6 % HES 130/0.4 infusion. Pulse rate (PR) was recorded automatically using a sphygmomanometer. Blood pressure and PR were taken after 5 min of rest in supine position. SpO_2 was taken from pulse oximetry and body temperature was measured in axillary. The subjects were asked nonleading questions (e.g., 'How do you feel?') to assess tolerability and adverse events at all scheduled time points during the study. Adverse events mentioned spontaneously by the subject were also recorded throughout the study.

Statistical analysis

Since this study was primarily aimed to describe the pharmacokinetics of 6 % HES 130/0.4, valid plasma concentration data of 12 subjects were considered sufficient to derive estimates of adequate reliability. Descriptive statistics were calculated for each parameter, namely, number of subjects (N), arithmetic mean, standard deviation (SD), and minimum, median, maximum, and geometric mean with corresponding CV. The evaluation of safety data using descriptive statistics included laboratory data (hematology parameters, coagulation tests, clinical chemistry, urine pH, and urinalysis), vital signs, 12-lead ECG, and adverse events.

Results

All 12 subjects were included in both the safety and the pharmacokinetics analysis set. Means (ranges) of demographic and baseline values were age 24 (20–31) years, height 1.71 (1.62–1.79) m, weight 61.8 (57–72) kg, body mass index 21.1 (18.6–23.5) kg/m^2, systolic blood pressure 108 (99–117) mmHg, diastolic blood pressure 56 (51–63) mmHg, mean arterial blood pressure 73 (68–80) mmHg, PR 53 (42–69)/min, SpO_2 98.0 (97–99) %, and body temperature 36.2 (35.9–36.7) °C. No abnormal findings were reported for medical history or 12-lead ECG at screening/baseline.

Pharmacokinetic analysis

Plasma concentration of HES 130/0.4 was highest at the end of infusion and decreased biphasically (Fig. 1). It was quantifiable in 8 subjects up to 48 h after end of infusion, but in none of all 12 subjects 72 h after the end of infusion.

Results for pharmacokinetic parameters (Table 1) were derived by applying the model-independent approach as well as by fitting a two-compartmental model. Comparable mean values can be recognized for the terminal half-life ($t_{1/2,z}$) with about 11 h and the model-based half-life for the beta-phase ($t_{1/2,\beta}$) with about 10 h.

Cumulative urinary excretion of HES until 72 h after infusion of 6 % HES 130/0.4 is shown in Fig. 2. The cumulative amount of HES excreted into urine after 72 h was 17.65 ± 1.56 g corresponding to 59.4 % of the administered dose of 29.7 g (contained in 500 mL 6 % HES 130/0.4). HES 130/0.4 was predominantly excreted within the first 24 h after administration, which already amounted to 16.97 g (96 % of excreted HES).

The time-course concerning alteration of the mean molecular weight (MW) of 6 % HES 130/0.4 in plasma until 48 h after infusion is shown in Fig. 3, including bottom and top fractions (after 72 h, all measurements

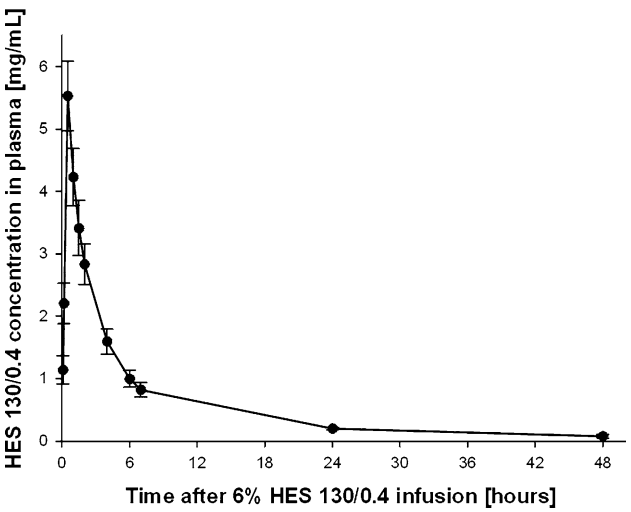

Fig. 1 Hydroxyethyl starch (HES) plasma concentration–time profile after 6 % HES 130/0.4 infusion (arithmetic mean ± SD, $n = 12$)

Table 1 Descriptive statistics for pharmacokinetic parameters ($n = 12$)

	Arithmetic mean ± SD	Median (range)	Geometric mean (CV)
Model independent			
AUC (mg/ml h)	26.72 ± 3.75	26.15 (20.7–33.2)	26.48 (14.1 %)
C_{max} (mg/ml]	5.53 ± 0.55	5.46 (4.77–6.42)	5.51 (10.0 %)
$AUC_{(0–tn)}$ (mg/ml h)	24.83 ± 3.77	24.31 (18.6–30.8)	24.56 (15.5 %)
$t_{1/2,z}$ (h)	10.92 ± 1.98	11.91 (8.10–13.08)	10.74 (19.6 %)
CL (l/h)	1.14 ± 0.16	1.15 (0.90–1.45)	1.13 (14.1 %)
V_{ss} (l)	12.95 ± 1.80	12.78 (9.90–16.35)	12.83 (13.9 %)
k_z (1/h)	0.066 ± 0.014	0.058 (0.053–0.086)	0.065 (19.6 %)
Two-compartmental modeling approach			
$t_{1/2,\alpha}$ (h)	1.12 ± 0.26	1.03 (0.87–1.74)	1.10 (20.6 %)
$t_{1/2,\beta}$ (h)	9.98 ± 2.38	9.23 (7.89–15.04)	9.76 (21.5 %)
$t_{1/2,c}$ (h)	2.80 ± 0.32	2.71 (2.47–3.45)	2.78 (10.9 %)
V_c (l)	4.76 ± 0.64	4.67 (4.02–6.32)	4.73 (12.9 %)

As it is generally assumed that pharmacokinetic parameters follow a log-normal distribution, geometric means and the corresponding coefficients of variation (CV) are also displayed. Furthermore, the CV represents a most convenient measure of variability (independent of scale)

AUC area under the observed concentration–time curve from start of infusion extrapolated to infinity, $AUC_{(0–tn)}$ area under the observed concentration–time curve from start of infusion up to the last time-point with measurable plasma concentration, C_{max} observed peak concentration, $t_{1/2,z}$ terminal half-life calculated as $-\ln(2)/k_z$, *CL* total plasma clearance calculated as dose/AUC, V_{ss} volume of distribution at steady state, k_z terminal rate constant derived from the log-linear regression on the terminal phase, $t_{1/2,\alpha}$ half-life for alpha phase, $t_{1/2,\beta}$ half-life for beta phase, $t_{1/2,c}$ half-life for drug elimination from central compartment, V_c volume of distribution of first (central) compartment

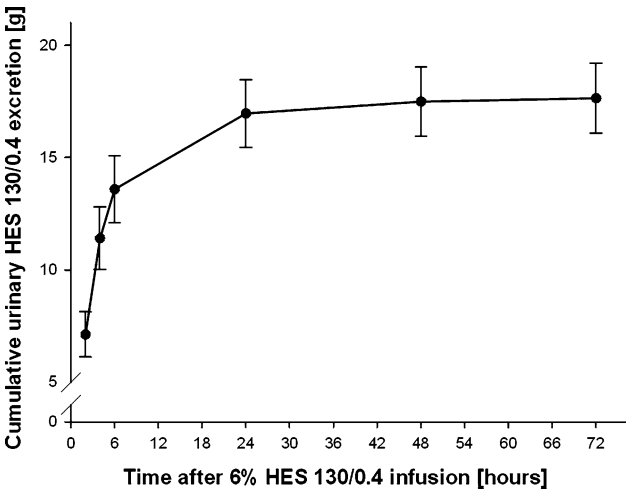

Fig. 2 Cumulative urinary excretion of HES after 6 % HES 130/0.4 infusion (arithmetic mean ± SD, $n = 12$)

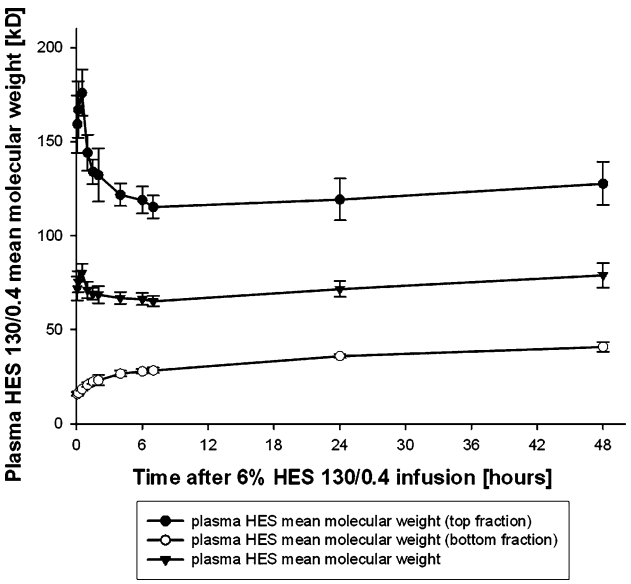

Fig. 3 Plasma mean molecular weight of HES (kDa) after 6 % HES 130/0.4 infusion (arithmetic mean ± SD, $n = 12$)

were below the quantification limit). The mean MW of the original 6 % HES 130/0.4 decreased from 130 to 80.2 kDa at the end of infusion. From 5 min to 48 h after start of infusion, mean MW varied between 65.2 kDa (at 7 h) and 80.2 kDa at 30 min. Mean MW of the top fraction clearly decreased from 176.0 kDa at end of infusion to 115.3 kDa after 7 h, and mean MW of the bottom fraction continuously increased from start of infusion until 48 h.

Figure 4 shows the arithmetic mean of the top fraction of HES 130/0.4 MW in urine over 72 h after 6 % HES 130/0.4 infusion. Continuous increases over the entire time-course were observed. On average, α-amylase was 58.8 ± 14.5 IU/l at baseline and 64.3 ± 15.4 IU/l at the end of infusion. It then clearly increased to 125.3 ± 21.5 IU/l after 7 h and returned to 65.7 ± 14.6 IU/l at 72 h.

Safety results

During the course of this study, no deaths and no serious adverse events occurred. A total of 31 adverse events were observed in 12 volunteers, none of which were reported by

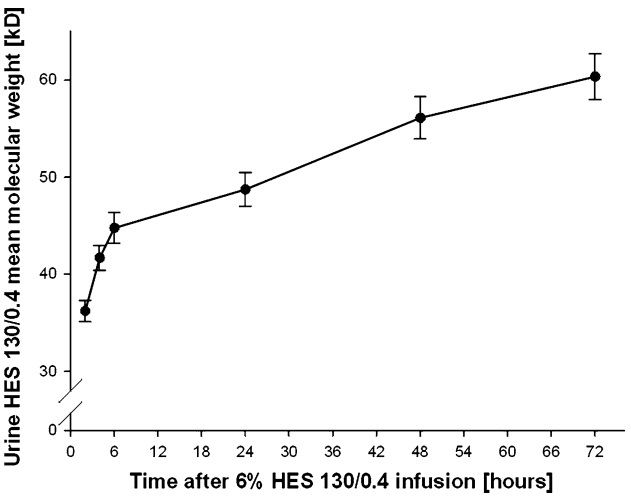

Fig. 4 MW top fraction in urine (kDa) of HES after 6 % HES 130/0.4 infusion (arithmetic mean ± SD, $n = 12$)

the subjects themselves but rather presented as abnormal laboratory parameters. Hemodilutions, which were reported in this study for all subjects, were expected as a result of the volume infusion of 500 ml 6 % HES 130/0.4, and were associated with changes in the laboratory parameters shown in Table 2. White blood cell count was increased in 1 subject and decreased in 2 subjects. Seven hemodilutions persisted after 72 h but required no further follow-up because of the lack of clinical relevance. Hematocrit values also decreased temporarily from baseline (45.07 ± 1.12 %) to 40.37 ± 1.09 % measured 30 min after of 6 % HES 130/0.4 infusion, but remained within the reference range during the entire study period. Prolonged activated partial thromboplastin time (aPTT) was reported in 6 volunteers; all of these persisted after 72 h but no follow-up was required as they were classified as not related to 6 % HES 130/0.4 administration and were not of clinical relevance.

In five volunteers, blood glucose levels appeared increased 7 h after start of 6 % HES 130/0.4 infusion, which was after lunch time. At the subsequent measurement (24 h) values had returned to within normal range (80–112 mg/dl). The levels were assessed as not being related to 6 % HES 130/0.4 administration and were clinically not relevant.

No abnormalities were reported for vital signs, 12-lead ECG, and physical examination. There were no abnormal findings with respect to local and systemic tolerance.

Discussion

In this open-label, uncontrolled, single-center study, 12 healthy male Japanese volunteers received a single 500 ml 6 % HES 130/0.4 infusion over 30 min to investigate the pharmacokinetics and safety of the drug.

Highest plasma concentrations were reached at end of infusion, decreased following a biphasic manner, and returned below the LOQ after 48 h in 4 subjects and after 72 h in the remaining 8 subjects.

Comparison of single-dose pharmacokinetics in Japanese volunteers with Caucasian subjects [8] reveals a smaller volume of distribution in Japanese volunteers, which is reported as 4.8 l compared to 5.9 l in Caucasians. Accordingly, systemic exposure of HES was higher in Japanese than in Caucasian subjects (as expressed by AUC and C_{max}). A single dose of 6 % HES 130/0.4 (26.3 g) administered to healthy Caucasian volunteers resulted in a mean C_{max} of 3.7 mg/ml and a mean AUC of 14.3 mg/ml h.

Since 6 % HES 130/0.4 is administered intravenously for volume expansion, pharmacokinetic parameters describing drug elimination and metabolization have major relevance. These parameters were comparable between Japanese and Caucasian healthy subjects, namely, plasma elimination half-life (11–12 h), renal excretion (about 60 %), and transition of mean molecular weight of HES in

Table 2 Laboratory parameters (arithmetic mean ± SD, $n = 12$)

	Time course after HES 130/0.4 infusion				
	Baseline	30 min	7 h	24 h	72 h
Hemoglobin (g/dl)	15.5 ± 0.4	13.8 ± 0.4	14.5 ± 0.5	15.0 ± 0.6	15.2 ± 0.5
Hematocrit (%)	45.1 ± 1.1	40.4 ± 1.1	42.3 ± 1.5	43.6 ± 1.4	44.7 ± 1.8
PT (s)	13.8 ± 0.6	15.0 ± 0.7	14.3 ± 0.7	13.8 ± 0.6	14.1 ± 0.5
aPTT (s)	38.8 ± 4.9	39.6 ± 5.2	39.7 ± 4.8	40.0 ± 4.4	40.9 ± 4.4
Alkaline phosphatase (IU/l)	187.8 ± 50.6	163.6 ± 40.9	195.1 ± 51.1	185.6 ± 48.4	192.8 ± 53.3
ALT (IU/l)	16.8 ± 7.0	14.3 ± 5.4	14.3 ± 5.5	15.4 ± 5.9	17.5 ± 7.3
AST (IU/l)	16.2 ± 5.3	13.3 ± 3.9	14.1 ± 3.0	15.4 ± 3.5	16.6 ± 4.6
LDH (IU/l)	122.9 ± 22.9	99.1 ± 15.0	111.3 ± 30.2	115.5 ± 19.4	116.5 ± 16.5
α-Amylase (IU/l)	58.8 ± 14.5	64.3 ± 15.4	125.3 ± 21.5	81.6 ± 17.9	65.7 ± 14.6
Albumin (g/dl)	4.1 ± 0.2	3.5 ± 0.2	3.8 ± 0.2	4.2 ± 0.2	4.4 ± 0.2
Glucose (mg/dl)	86.4 ± 4.0	–[a]	115.3 ± 11.3	87.6 ± 3.7	88.5 ± 3.8

[a] Not assessed at this time point

plasma (70–80 kDa), as well as the top fraction in urine (50–60 kDa). In particular, the similar urinary excretion rates and top fractions of the molecular weight of HES in urine showed that the renal elimination and the renal threshold to excrete HES 130/0.4 molecules were highly comparable between the ethnic groups. Data from repetitive infusions of 10 % HES 130/0.4 to healthy Caucasian volunteers [3] or single-dose infusion of 6 % HES 130/0.4 to Caucasian patients with renal impairment [9] further support that renal elimination rates do not significantly deviate from the data presented in this Japanese trial.

With respect to in vivo molecular weight after infusion of HES 130/0.4 it is important to note that the decrease in molecular weight occurs faster than after HES 200/0.5, which explains the maintenance of colloid-osmotic pressure at lower plasma concentrations [6]. As a consequence, similar hemodynamic effects were observed during surgery in a study after preoperative exchange of large volumes of blood with either 6 % HES 130/0.4 or 6 % HES 200/0.5 [7]. Finally, the lower in vivo molecular weight of HES 130/0.4 was associated with a lower effect on sensitive coagulation parameters [5, 6].

Single-dose administration of 500 ml 6 % HES 130/0.4 was safe and well tolerated by subjects of Japanese ethnicity. No adverse events were reported by the subjects themselves, but some were apparent from laboratory parameters related to infusion volume (hemodilution) that were not clinically relevant. Increased α-amylase levels are known nonpathological physiological reactions [10, 11] toward HES. As expected, increased α-amylase levels were reported 7 h after infusion and returned to baseline values at 72 h [10, 11]. Overall, safety results were comparable to the study conducted in healthy Caucasians [8], albeit no headaches were reported by Japanese subjects.

Since the objective of this trial was to investigate pharmacokinetics of a single infusion of 500 ml 6 % HES 130/0.4 in Japanese healthy male volunteers, the study was performed in an exploratory, noncontrolled manner. Generally, a placebo control group is considered to increase specificity of the safety and tolerability assessment of the study drug because it aids identification of adverse events that are more likely to be related to study conditions rather than to the test medication. However, critical safety issues were not expected to arise based on previous information, and actually a placebo group would not have provided any additional insight into the drug's safety profile in this study. The trial has limited informative value with regard to comparisons between Japanese and Caucasian subjects because these were based on historical controls. Nevertheless, the low variability of pharmacokinetic parameters derived in this study, as expressed by small coefficients of variation (mostly below 20 %), implies a high degree of credibility and reliability of study results.

In conclusion, there are no safety concerns with regard to single-dose administration of 500 ml 6 % HES 130/0.4 (Voluven) infusion in subjects of Japanese ethnicity. A rapid renal excretion of 6 % HES 130/0.4 was observed within 24 h after drug administration, accounting for 96 % of the total amount excreted, which was 59.4 % of the applied dose.

A comparison with pharmacokinetic data derived from Caucasians using the same model did not reveal significant differences to Japanese and confirmed the good tolerability of 6 % HES 130/0.4 (Voluven 6 %) in both ethnic groups.

Acknowledgments We thank Dr. Fukase/Kouryokai CPC Clinic Kagoshima for conducting the clinical study.

Conflict of interest Voluven® is a product of Fresenius Kabi. Dr. Bepperling is an employee of this company, and Dr. Miyao is a Medical Consultant to this company.

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