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KINETICS OF HYDROXYETHYL STARCH[1] IN HORSES

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SUMMARY

In a controlled study, the distribution and elimination kinetics of hydroxyethyl starch as well as clinically relevant parameters were determined in horses. The half-life of the first phase was 5.59 hours, that of the second phase 122.22 hours. During the first phase, hydroxyethyl starch persisted almost exclusively intravascularly. The results of this study are largely in agreement with those in human beings. Thus, routes of elimination, duration of plasma-expanding action, distribution volume and redistribution kinetics in horses and human beings are very similar. However, the elimination kinetics of the second phase and the behavior of serum amylase appear to be equine-specific. Coagulation is barley influenced by the administration of hydroxyethyl starch. The results of this study confirm that hydroxyethyl starch is very suitable for use as a plasma-expander in horses.

KEY WORDS: horse – plasma expander – kinetics – coagulation – plasma viscosity

KINETIK VON HYDROXYÄTHYLSTÄRKE BEIM PFERD

In einer kontrollierten Untersuchung wurden die Verteilungs- und Ausscheidungskinetik von Hydroxyäthylstärke sowie klinisch relevante Parameter beim Pferd untersucht. Die Halbwertszeit der 1. Phase liegt bei 5.59 Stunden, die der 2. Phase bei 122.22 Stunden. Während der ersten Phase verweilt die Hydroxyäthylstärke fast ausschliesslich intravasal. Die vorgestellten Daten stimmen weitgehend mit den humanmedizinischen überein. So sind die Eliminationswege, die Dauer der Volumenwirksamkeit, das Verteilungsvolumen und die Umverteilungskinetik fast gleich beim Menschen. Die Ausscheidungskinetik der zweiten Phase sowie das Verhalten der Serumamylase scheinen dagegen pferdespezifisch zu sein. Die Gerinnung wird durch die Verabreichung von Hydroxyäthylstärke kaum beeinflusst. Die Resultate dieser Untersuchung bescheinigen der Hydroxyäthylstärke eine gute Verwendbarkeit als Plasmaexpander beim Pferd.

SCHLÜSSELWÖRTER: Pferd – Plasmaexpander – Kinetik – Gerinnung – Plasmaviskosität

INTRODUCTION

he application of hydroxyethyl starch (HES) as a plasma xpander in horses for the treatment of shock and volume abilization has been repeatedly described (*Deegen,* 1975; *ɔier* and *Meagher,* 1989; *Hermann* et al. 1990; *Piacenza* and *'aberstroh,* 1990). However, no exact kinetic data on the use f HES in horses are available. The objective of this study was examine the kinetics of HES in horses.

MATERIAL AND METHODS

Animals and study design

Horses: Five Swiss warmbloods (2 geldings and 3 mares) between 7 and 13 years of age were used in this study. The body weight of the horses was between 520 kg and 620 kg. The horses were examined clinically shortly before and immediately after the study and hematological and serum chemistry evaluations were performed. All horses were clinically healthy at the start of this study and none had received any medication. The horses were familiarized with their new environment 4 days prior to the study. During the study they were fed and watered as usual and either had daily access to pasture or were ridden lightly each day for one hour.

[1] *HAES-steril® 10%, Fresenius AG, CH-6370 Stans*

Hematological evaluation: Blood samples were collected before infusion of HES (pre-infusion) and at the following times (hours) after initiation of infusion: ½, 1, 2, 3, 4, 6, 8, 12, 24, 48, 240. The following parameters were determined: HES concentration, hematocrit, plasma protein, serum albumin, plasma viscosity, serum amylase and coagulation parameters (prothrombin time, partial thromboplastin time and thrombin time). Blood samples at 6 and 8 hours were not collected in horse 1 because this horse had been previously examined as a screening animal. In horse 1, the HES analysis of the blood sample collected 48 hours after initiation of infusion could not be performed due to technical reasons.

Urinalysis: At time 0, the horses were catheterized, provided they did not urinate spontaneously. Urine was collected over a 24 hour period with a urinary collecting device (net with a plastic bag) similar to that used for doping controls. At 12 and 24 hours after initiation of infusion, the volume of urine was measured and a sample of 30 ml was drawn for the determination of HES concentration. At 48 and 240 hours after initiation of infusion, either spontaneously voided urine or urine obtained via a catheter was collected for analysis.

Administration and dosage of HES: Immediately after the zero value blood samples were drawn, the horses received HES via an indwelling jugular vein catheter[2]. The dosage was 0.8 g/kg body weight which corresponds to 8 ml/kg body weight of infusion solution. Hydroxyethyl starch was administered from a 4 l infusion bag within 30 minutes, using an infusion pump[3] (0.27 ml/kg/min.). The dosage was adjusted to 100 kg body weight. This dosage was lower than that used in human medicine (up to 20 ml/kg body weight/hour; *Anonymous,* 1987); however, it does correspond approximately to the dosage and infusion rate used by *Hermann* et al. (1990) in clinical use in horses.

Muscle biopsy: On day 10, a muscle biopsy (approximately 500 mg) was obtained from the caudal thigh muscles after local anesthesia; the concentration of HES was determined for the evaluation of the retention behavior of HES.

Fecal analysis: The feces of two horses were collected from the rectum prior to and 24 hours after initiation of infusion and examined for the concentration of HES.

Sample management and storage: Hematocrit, total solids (measured with a refractometer), and plasma viscosity were determined immediately after collecting each blood sample. The other samples were frozen at –30 °C for subsequent analyses.

Laboratory test methods

Hydroxyethyl starch: Hydroxyethyl starch concentration was determined in serum, urine, feces and muscle using the hexokinase/glucose-6-phosphate dehydrogenase method (*Wikaryczyk,* 1981) in the laboratory of the Center for Anesthesiology and Resuscitation, Wolfgang Goethe University Frankfurt a. Main.

Hematocrit: The hematocrit was determined after centrifugation of anticoagulated (EDTA) blood in a laboratory centrifuge[4].

Plasma protein concentration: Plasma protein concentration was determined refractometrically as well as by the Biuret method using an autoanalyzer[5].

Serum albumin: Serum albumin was determined using the the bromocresol green method and the above described analyzer, according to the manufacturer's instructions.

Plasma viscosity: Plasma viscosity was measured using a fully automated capillary viscosimeter[6]. The mean value was determined from two measurements. To date, none of the reference values provided (*Archer* and *Allen,* 1970; *Mason* and *Kwork,* 1977; *Dintenfass* and *Fu-Lung,* 1982; *Allen* and *Blackmore,* 1984; *Amin* and *Sirs,* 1986) have been measured by the capillary viscosimeter described above. Therefore, at the start of the study reference values were determined in 80 clinically healthy horses, 4 to 25 years of age (mean age 10.5 years). These horses came from 8 different locations in Switzerland; the horses were clinically healthy and had not received medication for at least 14 days prior to blood collection. Ten ml of anticoagulated (EDTA) blood was collected from 49 geldings, 30 mares and one stallion. Plasma viscosity was measured within 2 hours after plasma collection.

Serum amylase: The determination of serum amylase was performed using a kinetic UV test and the previously described analyzer according to the manufacturer's instructions.

Coagulation analyses: Prothrombin time, partial thromboplastin time and thrombin time were determined at 0, 12, 24, 48 and 240 hours after initiation of infusion. Determinations were performed on plasma from blood containing Na-citrate as an anticoagulant and using a coagulation analyzer[7].

[2] *14 G 6 Dauerkatheter, Becton Dickinson, CH-4002 Basel*
[3] *Baxa, Schoch Electronics, CH-8105 Regensdorf*
[4] *Hettich Hämatokrit 2011, Hettich, D-7200 Tuttlingen*
[5] *Cobas Mira, Hoffmann-La Roche, CH-4002 Basel*
[6] *Rheomat, Fresenius AG, CH-6370 Stans*
[7] *Cobas Fibro, Hoffmann-La Roche, CH-4002 Basel*

Statistics

Graphs: Blood parameters during the experimental period were presented graphically; individual HES concentrations for all horses are listed in a table. Urinary excretion of HES was calculated by multiplying the concentration by the amount of urine voided during the first 12 and 24 hours, respectively. Results are presented graphically and also computed in terms of percentage of the total amount of HES infused. The box plot method (*Eggenberger* and *Thun,* 1984) was used to present reference values for plasma viscosity.

Statistical analysis: The calculation of the pharmacokinetic data was carried out with the two compartment model (*Derendorf* and *Garret,* 1987) with 0 order invasion (continuous drip infusion during 30 minutes) and 1st order elimination with a pharmacological computer modelling program[8] according to the following equation:

$Cp = a*e^{-\alpha t}+b*e^{-\beta t}$.

The following kinetic parameters of HES were calculated (*Derendorf* and *Garret,* 1987):

- Elimination constants α and β
- Half-lives $t_{½\alpha}$ and $t_{½\beta}$
- Transfer rates k_{10}, k_{12} and k_{21}
- Transfer half-lives $t_{½\,(10)}$, $t_{½\,(12)}$ and $t_{½\,(21)}$
- Distribution volume V_c

The Friedmann two-way of analysis by ranks for related samples (*Sachs,* 1984a) was used to test the null hypothesis H_0 that the experimental values were not different from reference values. When H_0 was rejected, a test by Wilcoxon-Wilcox (*Sachs,* 1984b) was used for comparison of individual experimental values with the initial measurments. A goodness-of-fit test using 9 categories was employed to test the agreement between the observed distribution of the plasma viscosity and a normal distribution (*Werner,* 1984).

The Friedmann analysis and the goodness-of-fit test were computed using a statistic program[9]. The Wilcoxon-Wilcox test was calculated with the method described by *Sachs* (1984b). To establish reference values for plasma viscosity, mean, standard deviation, median (= 50th percentile), and 2.5th, 25th, 75th and 97.5th percentiles were calculated. For all analyses, $p < 0.05$ was significant.

[8] *MKMODEL, Vers. 4.0, N. Holford, Biosoft, Cambrige, UK.*
[9] *Statgrafics, Vers. 2.6., STSC Inc., USA.*

RESULTS

Hydroxyethyl starch concentration and its calculated values

Serum (Table 1, Fig. 1): The concentration and mean value of HES and the percentage of the HES volume still present compared to 0.5 hours (end of infusion) are presented in Table 1. The highest concentration of HES (11.68 ± 0.58 mg/ml) in serum was measured immediately after the end of the infusion. Subsequently, the serum concentration of HES continued to drop during the entire period of observation

Fig. 1: Concentration of HES (g/l) in the serum of five horses before (0 hours) and after the intravenous administration of HES (0.8 g/kg body weight).

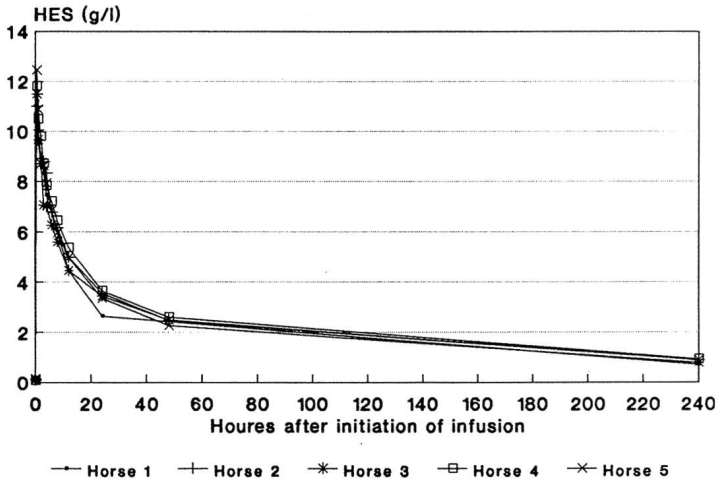
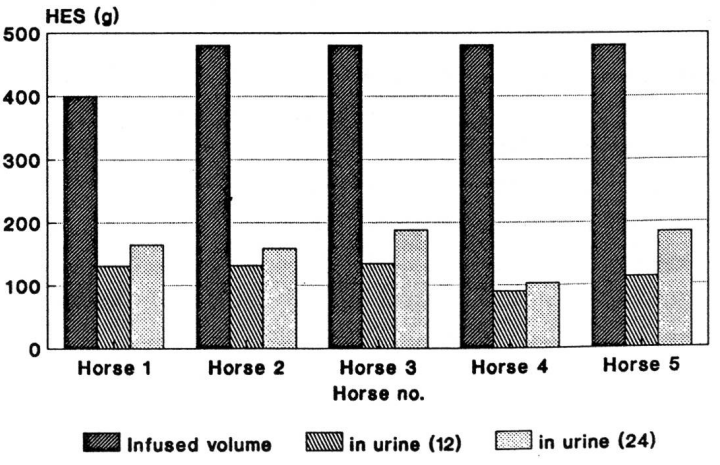


Fig. 2: Amount of HES (g) infused and absolute amount of HES (g) in the total amount of urine voided in the first 12 and 24 houres after intravenous administration of HES (0.8 g/kg body weight) in five horses.



Tab. 1: Changes in HES concentration (mg/ml), means and % of the initial HES concentration in the serum of five horses following a 30 minute infusion

Time (hours)	Horse no.					Mean value	(%)
	1	2	3	4	5		
0	0.05	0.08	0.14	0.06	0.09	0.08	——
0.5	11.19	11.01	11.94	11.82	12.44	11.68	100.00
1	10.19	10.05	9.67	10.48	10.88	10.25	87.76
2	9.05	8.91	8.72	9.80	9.72	9.24	79.11
3	8.32	8.79	7.07	8.72	8.64	8.31	71.15
4	7.46	8.33	7.04	7.84	7.93	7.72	66.10
6	——	6.78	6.26	7.22	6.87	6.78	58.05
8	——	6.18	5.60	6.46	5.97	6.05	51.80
12	4.46	5.00	4.45	5.37	4.97	4.85	41.52
24	2.65	3.56	3.44	3.66	3.35	3.33	28.51
48	——	2.47	2.49	2.61	2.27	2.46	21.06
240	0.70	0.89	0.89	0.92	0.77	0.83	7.11

Tab. 2: Elimination constants, elimination half-lives, transfer rates, transfer half-lives and distribution volumes of HES in horses and in human beings

	Horses	Human beings
α	0.1238 ± 0.0161/h	0.207/h
$t_{1/2\alpha}$	5.59 ± 0.73 h	3.35 h
β	0.00567 ± 0.0006/h	0.0226/h
$t_{1/2\beta}$	122.22 ± 11.95 h	30.61 h
k_{12}	0.07272 ± 0.0071/h	0.0841/h
$t_{1/2\,(12)}$	9.53 h	8.24 h
k_{21}	0.03856 ± 0.0038/h	0.0481/h
$t_{1/2\,(21)}$	17.92 h	14.41 h
k_{10}	0.01812 ± 0.00181/h	0.0974/h
$t_{1/2\,(10)}$	38.25 h	7.12 h
V_C	72.5 ml/kg	81.3 ml/kg

(Fig. 1). All HES had not been eliminated from the serum of any horse 240 hours after initiation of infusion. The calculated pharmacokinetic values are reported in Table 2 and are compared with the results in human beings (*SMD Medizin Data GmbH,* 1990).

Concentration of HES in urine (Fig. 2): The concentration of HES in urine at time 0 (pre-infusion) was between 0.11 mg/ml and 0.40 mg/ml in all horses. Twelve hours after initiation of infusion, an average of 26.07% (18.71%–32.59%) of the HES volume infused was detectable in urine. After 24 hours, the mean value was 34.61% (21.41%–41.13%). At the end of the study (after 240 hours) the absolute values were between 0.21 mg/ml and 0.53 mg/ml.

Concentration of HES in feces: The initial concentration of HES was 0.62 mg/g feces in horse 4 and 0.96 mg/g feces in horse 5. The concentration of HES after 24 hours was 0.44 mg/g feces in horse 4 and 0.94 mg/g feces in horse 5.

Concentration of HES in muscle biopsies: Hydroxyethyl starch concentrations in muscle biopsies at day 10 of the study were between 1.38 mg/g muscle and 2.98 mg/g muscle.

Laboratory parameters

The determined laboratory parameters are listed in Tables 3–5 and depicted in Figures 3–10.

Hematocrit (Fig. 3): There was an initial drop in the hematocrit of between 25% and 34.5%, of the pre-infusion value; it did not return to the pre-infusion value before 24 hours. Except for one horse (no. 2) the lowest hematocrit value was measured at 1 hour after initiation of infusion; in horse 2, the hematocrit was lowest 2 hours after initiation of infusion. After reaching its lowest value, the hematocrit continued to increase. The differences between the hematocrit values during the course of the study were highly significant ($p < 0.001$); there was a highly significant decrease in the hematocrit values 1 hour after initiation of infusion ($p < 0.01$) and a significant decrease in the hematocrit values 2 hours after initiation of infusion ($p < 0.05$) compared to the pre-infusion value.

Plasma proteins (Figures 4 and 5): The plasma protein values measured using a refractometer (Fig. 4) did not change significantly during the study ($p > 0.05$), whereas the values determined according to the Biuret method (Fig. 5) showed a pronounced decrease after the end of infusion. The values 1 hour after initiation of infusion were significantly decreased ($p < 0.05$) compared to the initial values, and the differences during the experimental period were highly significant ($p < 0.001$).

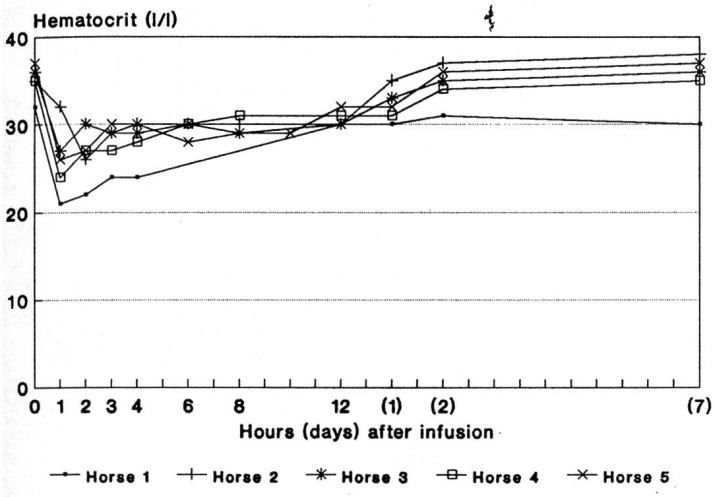
Reference values of plasma viscosity (Table 4 and Fig. 6): Plasma viscosity values in horses were not normally distributed ($p < 0.01$). Since the reference range should contain 95%

Tab. 3: Hematocrit, plasma protein, serum albumin, serum amylase and plasma viscosity in 5 horses following a 30 minute infusion of HES (8 ml/kg body weight), and reference ranges in [])

Time	0	1	2	3	4	12	24	48	240
Hematocrit (1/1)[a] [28–41]									
x	35.0	26.0[2]	26.4[1]	27.8	28.2	30.0	32.2	34.6	35.2
SD	1.67	3.63	2.58	2.14	2.23	0.63	1.72	2.06	2.79
Plasma protein, by refractometry (g/l)[b] [52–65]									
x	60.2	58.8	60.4	60.4	60.2	61.0	61.6	61.6	64.2
SD	1.67	1.47	0.80	2.06	2.04	1.79	2.58	3.38	5.0
Plasma protein, Biuret (g/l)[a] [55–75]									
x	68.2	58.06[1]	60.7	61.4	60.9	64.2	67.3	67.9	72.7
SD	5.56	1.19	1.18	2.50	2.23	2.32	2.72	4.23	5.63
Serum albumin (g/l)[a] [28–38]									
x	37.9	30.6[1]	32.0[1]	33.5	32.2	35.8	34.7	37.5	38.1
SD	1.44	2.31	2.56	1.68	2.09	1.54	3.36	2.92	1.79
Plasma viscosity (mPas)[a] [1.16–1.41]									
x	1.22	1.37[1]	1.37[1]	1.35[1]	1.33	1.27	1.26	1.25	1.35
SD	0.02	0.02	0.01	0.02	0.03	0.02	0.03	0.04	0.19
Serum amylase (U/l)[b] [16–42]									
x	45.4	33.2	35.0	36.8	37.2	39.4	37.6	41.2	39.8
SD	5.68	6.11	8.0	5.60	5.91	3.72	7.42	7.19	12.01

[a] *Friedmann-test: $p < 0.001$*
[b] *Friedmann-test: not significant*
[1] *Wilcoxon-Wilcox-test: $p < 0.05$, compared with the initial value*
[2] *Wilcoxon-Wilcox-test: $p < 0.01$, compared with the initial value*

Fig. 3: The hematocrit of five horses before (0 hours) and after the intravenous administration of HES (0.8 g/kg body weight).



of the determined values (*Willer* and *Leopold,* 1989), we took the 2.5 and the 97.5 percentiles as reference limits and not the mean value ± 2 standard deviations; for this study this means a reference range of 1.16–1.41 mPas.

Plasma viscosity in the kinetic test (Fig. 7): Plasma viscosity increased immediately after the end of infusion and subsequently decreased continuously to the initial values. The differences in plasma viscosity at the various times were statistically highly significant ($p < 0.001$). Plasma viscosity 1, 2, and 3 hours after initiation of infusion was significantly increased compared to the initial values ($p < 0.05$). Another

Fig. 4: The concentration of plasma protein (g/l) of five horses, as determined by refractometry, before (0 hours) and after the intravenous administration of HES (0.8 g/kg body weight).

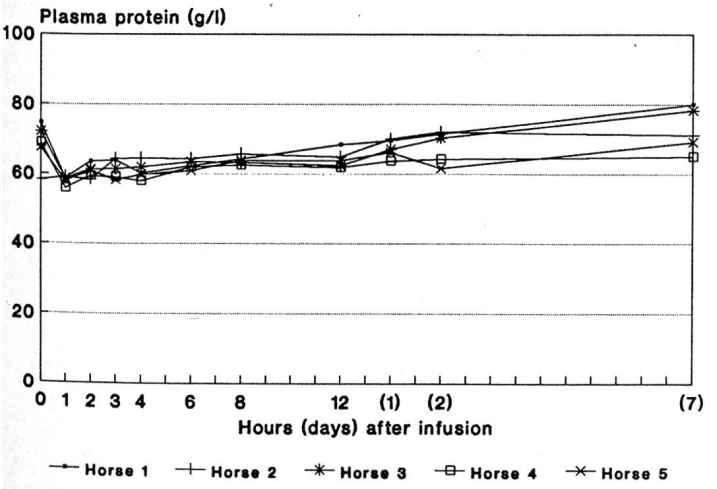


Fig. 5: The concentration of plasma protein (g/l) of five horses, as determined by the Biuret method, before (0 hours) and after the intravenous administration of HES (0.8 g/kg body weight).

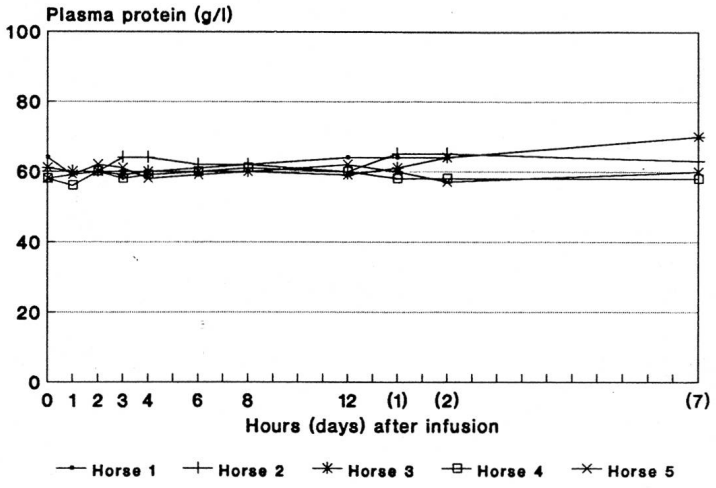
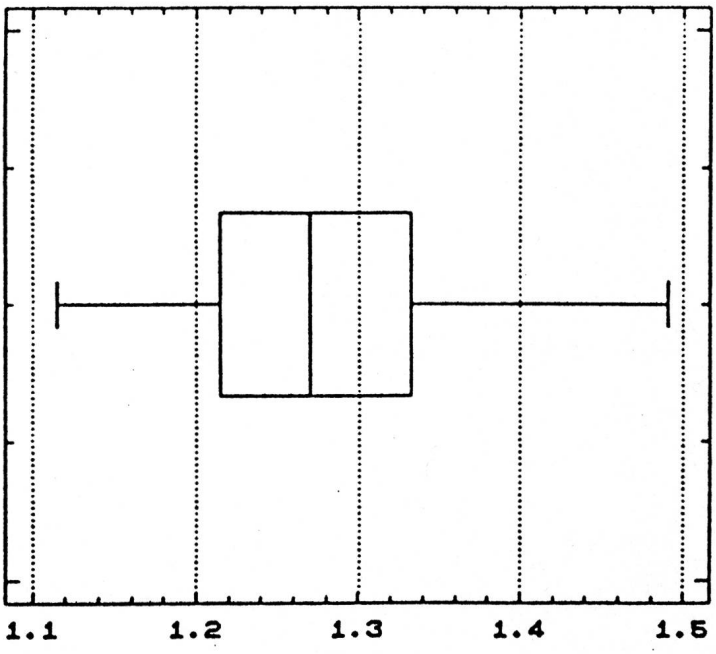


Fig. 6: Plasma viscosity (mPas) of 80 reference horses



Tab. 4: Reference values of plasma viscosity (mPas) in 80 healthy horses

Mean value	1.27
Standard deviation	0.075
2.5th percentile	1.16
25th percentile	1.21
50th percentile (median)	1.26
75th percentile	1.33
97.5th percentile	1.41

Fig. 7: Plasma viscosity (mPas) of five horses before (0 hours) and after the intravenous administration of HES (0.8 g/kg body weight).

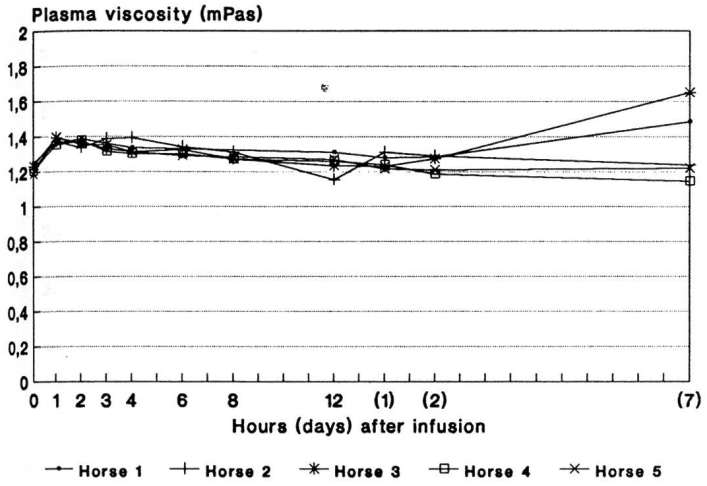
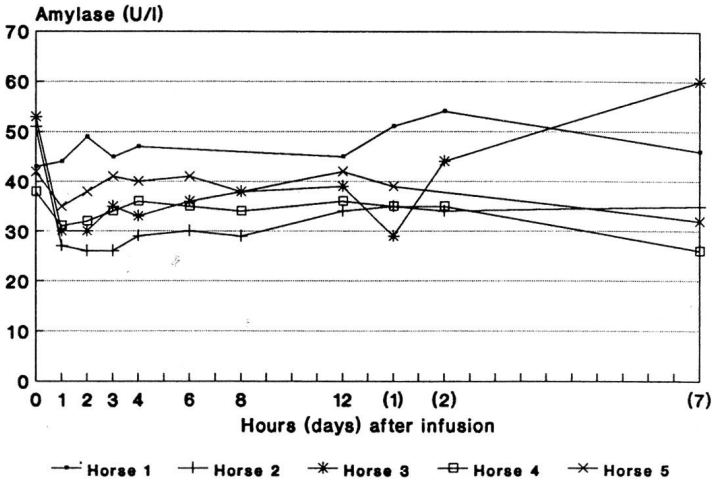


Fig. 8: Concentration of serum amylase (U/l) of five horses before (0 hours) and after the intravenous administration of HES (0.8 g/kg body weight).



increase in plasma viscosity between 48 and 240 hours after initiation of infusion occurred in horses 1 and 3.

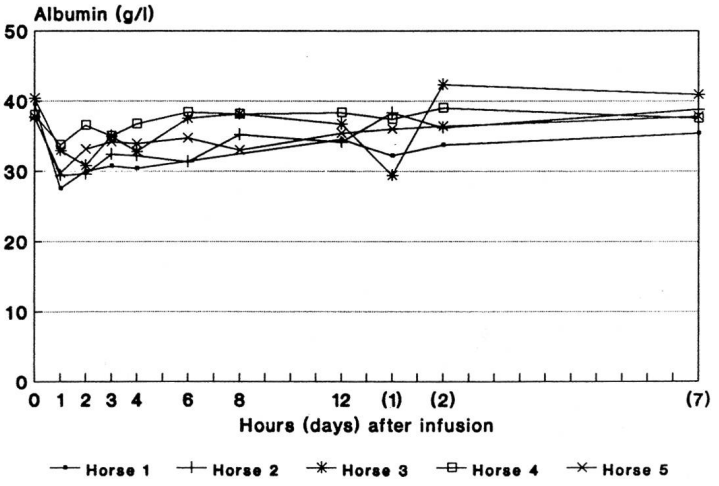
Serum amylase (Fig. 8): Serum amylase initially had a variable behavior; it increased minimally in horse 1, dropped markedly in horses 2 and 3 and decreased slightly in horses 4 and 5. Subsequently, amylase had a stationary course except for horse 3, in which it increased between 24 and 240 hours after initiation of infusion. The differences were statistically not significant at the 5% level.

Serum albumin (Fig. 9): The serum albumin concentration had a pattern of behavior similar to that of the plasma protein concentration determined according to the Biuret method. It reached a maximum low point immediately after the end of infusion and subsequently increased slowly. The differences were statistically highly significant ($p < 0.001$). The values 1 and 2 hours after initiation of infusion were significantly decreased compared to the initial value ($p < 0.05$).

Coagulation parameters (Table 5, Fig. 10): Changes in the prothrombin time and the partial thromboplastin time were not significant during the course of the study ($p > 0.05$). However, there was a significant change in the thrombin time during the experimental period ($p < 0.05$); 12 hours after initiation of infusion, the thrombin time was 2.42 seconds shorter, on average, than before infusion ($p < 0.05$).

Tolerance: The horses had no undesirable side-effects during infusion. On day 8 after infusion, horse 3 had thrombophlebitis of the distal jugular vein at the site where the catheter had been placed. This thrombophlebitis was treated systematically with non-steroidal anti-inflammatory drugs and locally with antiphlogistic ointments.

Fig. 9: Concentration of serum albumin (g/l) of five horses before (0 hours) and after the intravenous administration of HES (0.8 g/kg body weight).



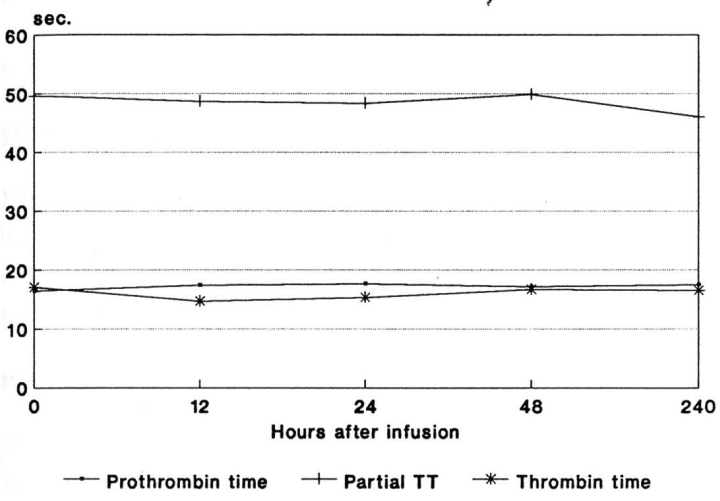
DISCUSSION

Serum concentration of HES

There were several similarities between the pharmacokinetic data of HES in human beings and in horses. The elimination constants of the α-phase in horses (0.207/h) and that of human beings (0.124/h) were very similar, whereas the elimination constant of the β-phase in horses (0.0057/h) was considerably lower than that in human beings (0.0226/h).

The half-lives of the α-phase ($t_{½\alpha}$) in horses (5.6 h) and in human beings (3.35 h) are remarkably similar according to

Fig. 10: Mean values of prothrombin time, partial thromboplastin time, and thrombin time of five horses before (0 hours) and after the intravenous administration of HES (0.8 g/kg body weight).



Tab. 5: Coagulation parameters in 5 horses following a 30 minute infusion of HES (8 ml/kg body weight), and reference ranges []

Time	0	12	24	48	240
Prothrombin time (sec.) [14.6–19.95]					
x	16.8	17.3	17.6	17.1	17.4
s	2.94	1.96	1.43	2.17	2.63
Partial thromboplastin time (sec.) [37.85–56.4]					
x	49.6	48.3	48.3	49.8	46.0
s	2.99	4.16	1.50	2.22	1.95
Thrombin time (sec.)[a] [12.1–21.2]					
x	17.1	14.7[1]	15.3	16.6	16.1
s	2.70	0.94	1.35	2.24	1.28

[a] *Friedmann-test: $p < 0.05$*

[1] *Wilcoxon-Wilcox-test: $p < 0.05$, compared with the initial value*

the results of this study. However, the half-life of the β-phase in horses (122.22 h) is significantly longer than in human beings (30.61 h). This suggests a specific HES metabolism with slower elimination kinetics in horses than in human beings. However, the observation period of the present study was three times longer (240 h) than in the studies conducted in human beings (72 h, *SMD Medizin Data GmbH,* 1990). Thus, the period of the terminal elimination phase in human beings was possibly underestimated and, consequently, the terminal half-life ($t_{½}\beta$) overestimated. *Wikarczyk* (1981) supports this assumption. In her study, there was still 15% of the infused HES concentration in the serum 10 days after the infusion; however, the HES was in a galenic form with a mean MW of 450 000, which does not allow a direct comparison. Considering the transfer rates k_{12} and k_{21} it is obvious that the values for horses and human beings are practically identical. Initially, HES is eliminated in horses approximately 2 times faster ($t_{½\alpha}$ = 5.59 h) than it is redistributed from the vascular system ($t_{½\,(10)}$). Thus, the active ingredient in the first phase is present almost only intravascularly. Only the transfer rate k_{10} is approximately 5 times smaller in horses than in human beings. The corresponding $t_{½\,(10)}$ is, thus, approximately 5 times longer. This is in agreement with the findings that $t_{½}\beta$ in horses is significantly longer than in human beings. The distribution volume of the initial or central compartment of 72.5 ml/kg body weight (or approximately 36 l per horse/500 kg body weight) corresponds indeed to the approximate blood volume of a horse of 500 kg body weight (*Eder,* 1987).

Elimination of HES via the urine

Analogous to man, the kidney is probably the main route of elimination of HES in horses (*Mishler,* 1980; *Förster* et al., 1981; *Köhler* et al., 1982). In the present study, 1/3 of the infused volume of HES was found in the urine 24 hours after starting the infusion. *Mishler* (1980) found between 50% and 66% of the volume of HES 200/0.5, administered in an almost equal dose (0.7g/kg BW) and at almost the same rate (0.28 ml/kg BW) in the urine of healthy people within the first 24 hours. *Förster* et al. (1981) found approximately 30% of the infused volume of a 6% solution of HES (mean molecular weight (MW) of 450 000) in the urine of healthy people after 24 hours. *Köhler* et al. (1982) found 53.7% of the infused volume in the urine of healthy people 24 hours after the administration of HES with the same galenic form used in this study. However, *Mishler* (1980) and *Köhler* et al. (1982) determined the concentration of HES using the Anthron method, which has been considered inadequate since 1981 according to *Wicarkzyk* (1981). In addition *Förster* et al. (1981) tested a HES solution with a higher molecular weight than the HES used in this study and thus, a direct comparison of the renal excretion values with values from human medicine is restricted.

HES concentration in feces

Since the values of the two fecal samples (0 and 24 hours) did not differ greatly, it must be assumed that fecal elimination of HES in horses in not an important route within the first 24 hours.

HES concentration in muscle biopsies

The HES concentrations measured in the muscle biopsies at day 10 of the study were higher than comparable values in rats (*Förster,* 1990). Thus, there may be traces of HES in muscles of horses 10 days after treatment.

Hematocrit

The hematocrit decreased substantially in all horses. This results from the volume-expansive effect of HES. *Hermann* et al. (1990) reported similar results both in therapeutical use and in a comparative study with two healthy horses; the hematocrit was substantially decreased during an approximately 2 hour period after infusion of HES. This must be considered when treating horses for shock. This effective period measured by the hematocrit allows a good volume control (*Mishler,* 1982), by continuing HES infusion in a shock patient, if required, without overhydrating him.

Plasma protein concentration

If the results of the two measurement methods used are compared, one receives diverging results. The plasma protein concentration determined according to the Biuret method were higher than those determined with a refractometer *(Kraft* and *Schillinger,* 1989). Refractometry is an unspecific method to quantify the concentration of total solids in plasma or serum, whereas the Biuret method specifically detects peptide bonds *(Kraft* and *Schillinger,* 1989). The results presented in this study therefore mean that the concentration of total solids remains constant with a decreasing protein concentration. If this concentration is used as a measure for the colloidal-osmotic pressure, it may be concluded that in the case of a substantial volume effect (relative decrease of the actual protein concentration) the colloidal-osmotic pressure during administration of HES remains unchanged. *Hermann* et al. (1990) reported plasma protein decreases of 5–13%, which were determined by refractometry. The reason for the plasma protein decreases in that study might have been attributable to other administered medication, particularly crystalloid infusion solutions.

Reference values of Plasma viscosity

Archer and *Allen* (1970) as well as *Mason* and *Kwork* (1977) and *Allen* and *Blackmore* (1984) determined plasma viscosity values at 25 °C. Therefore, their values are higher compared to those of this study. However, the values determined in this study were higher compared to those of *Dintenfass* and *Fu-Lung* (1982). This might have been due to the smaller population (n = 19), the specific group composition (only racing horses), the substantially lower average age (3 ± 1.30 years) and the use of a different measuring device (Couler-Harkness capillary viscosimeter).

In the present study, plasma viscosity was measured with a technique that was analogous to that used in a study in human medicine (*Jung* et al., 1986). In horses, the mean (1.27 versus 1.24 mPas) and the 95% confidence interval (1.16–1.41 mPas versus 1.14–1.34 mPas) were slightly higher than in human beings and, unlike in people, values were not normally distributed. In the studies of *Amin* et al. (1986) and *Dintenfass* and *Fu-Lung* (1982), the values for plasma viscosity were also in agreement with those in human medicine under analogous measuring conditions.

Plasma viscosity in the kinetic test

Plasma viscosity increased in all horses after the end of infusion but did not exceed the upper limit of the determined reference values. A decrease in plasma viscosity leads to an increased perfusion of the terminal vascular system (*Kiesewetter* and *Jung,* 1987). Thus, the results of this study signify that the terminal vascular system is less well perfused following HES infusion. Similar to another study (*Meister,* 1991), plasma viscosity remains unchanged when HES and crystalloid solutions (ratio HES: crystalloid solution = 1: 2–3) are administrated simultaneously.

Plasma viscosity depends essentially on the concentration of large molecular proteins, particularly from fibrinogen (*Archer* and *Allen,* 1970; *Dintenfass* and *Kammer,* 1977; *Allen* and *Blackmore,* 1984; *Jung* et al., 1986). The plasma viscosity of 1.65 mPas determined in horse 3, 240 hours after initiation of infusion, might have been associated with the elevated fibrinogen level (7 g/l) caused by thrombophlebitis. The plasma viscosity of 1.485 mPas determined in horse 1, 240 hours after initiation of infusion was probably also associated with the high plasma protein level (80 g/l). The reason for this elevated plasma protein value could not be determinated.

Serum albumin

The concentration curves of serum albumin and plasma protein had similar patterns, indicating that both parameters may reflect changes in the intravascular volume.

Serum amylase

The initial drop in serum amylase in 4 horses can be explained by the dilution effect after infusion of HES. Similar findings were reported in a study in which dogs were administered HES (*Jesch* et al., 1975). It was unclear why amylase increased slightly in horse 1. It was interesting to note that during this study, serum amylase usually remained constant and did not change significantly with time. It is known that in dogs (*Jesch* et al., 1975) and in human beings (*Köhler* et al., 1982), serum amylase increases after the dilution-induced decrease. This increase is explained by the formation of an enzyme substrate complex between HES and serum amylase. Serum amylase has a MW of 45 000 and is easily eliminated via the kidney. However, elimination of the HES/serum amylase complex is slow and accumulation of the complex in the serum results; this is of no clinical importance (*Köhler* et al., 1982). The molecular weight of serum amylase in animals is approximately 50 000 and elimination via the kidney appears to be analogous to that in human beings (*Schmidl* and *Forstner,* 1985). The results of this study, suggest that serum amylase does not form a complex with HES or that the HES molecules included in the complex have a size such that renal excretion occurs unhindered.

Coagulation parameters

The dosage of HES used in this study, had almost no influence on coagulation. The values in this study remained within the clinical reference ranges. Only 12 hours after initiation of infusion was the thrombin time slightly shorter. These results are in agreement with those in human medicine, in which HES has less influence on coagulation in comparison to Dextran *(Kiesewetter* and *Jung,* 1987; *Klose* et al., 1987). Thus, the prothrombin time during the experimental period remained stable and the partial thromboplastin time was characterized by an insignificant reduction 12 hours after initiation of infusion. The deviation in the thrombin time was still within our reference range of 12.1–21.2 sec. and, therefore, was clinically irrelevant. A decrease in the thrombin time was also reported in a study comparing HES and Dextran 40 in human beings (*Popov-Cenic* et al., 1977). However, in this study the decrease in thrombin time appeared to be due to the intraoperative hypercoagulability or the use of a different galenic form of HES (MW 450 000). In a study conducted by *Klose* et al. (1987), in which Dextran 40 was compared to HES 200/0.5, prothrombin time, partial thromboplastin time and thrombin time did not differ significantly, during the course of the study from those values determined before infusion.

Side-effects

Exept for the thrombophlebitis in horse 3, no undesirable side-effects were observed. The thrombophlebitis of the jugular vein, diagnosed at day 8, was probably associated with the administration of HES. However, after clinical use of HES in over 250 patients, the authors feel that HES was not responsible for the thrombophlebitis, because this HES preparation is particularly well-tolerated intravenously.

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La cinétique de l'hydroxyéthyle d'amidon chez le cheval

La distribution et la cinétique d'une solution d'hydroxyéthyle d'amidon ont été étudiées chez le cheval dans le cadre d'une étude contrôlée et certains paramètres d'importance clinique furent déterminés.

La demi-vie de la première phase se situe autour de 5,59 heures, celle de la deuxième phase 122,22 heures.

Durant la première phase la solution d'hydroxyéthyle d'amidon demeure presque entièrement dans l'espace intravasal. Les résultats présentés concordent avec ceux obtenus chez l'homme. Les voies d'élimination, la durée de l'effet volumique, le volume de distribution et la cinétique de redistribution sont presque identiques aux paramètres mesurés chez l'homme. La cinétique d'élimination de la deuxième phase et le comportement de l'alpha-amylase semblent cependant très spécifiques au cheval. La coagulation sanguine n'est pratiquement pas influencée par l'administration d'une solution d'hydroxyéthyle d'amidon. Les résultats obtenus permettent de prouver l'applicabilité d'une solution d'hydroxyéthyle d'amidon comme expanseur de plasma chez le cheval.

La cinetica dell'amidoidrossietilico nel cavallo

In un esperimento controllato sono state esaminate la cinetica di distribuzione e d'eliminazione dell'amidoidrossietilico. Il tempo di dimezzamento della la fase era 5,59 ore, quello della seconda fase 122,22 ore. Durante la prima fase l'amidoidrossietilico era quasi esclusivamente intravasale. I dati riscontrati coincidono con quelli attenuti in medicina umana. Le vie d'eliminazione, la durata dell'effetto di volume, il volume di distribuzione e la cinetica di ripartizione sono quasi identiche nell'uomo. La cinetica d'eliminazione della seconda fase ed il comportamento della alpha-amilasi appaiono invece essere specifiche nel cavallo. La coagulazione non viene influenzata dall'applicazione dell'amidoidrossietilico. I risultati di quest'esperimento dimostrano che l'amidoidrossietilico é utilizzabile come espansore del plasma nel cavallo.

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