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INSTITUTE REPORT NO. 456

Concentration and Molecular Size Distribution of Dextran in Serum from Rabbits and Dogs Infused with Hypertonic Saline Dextran

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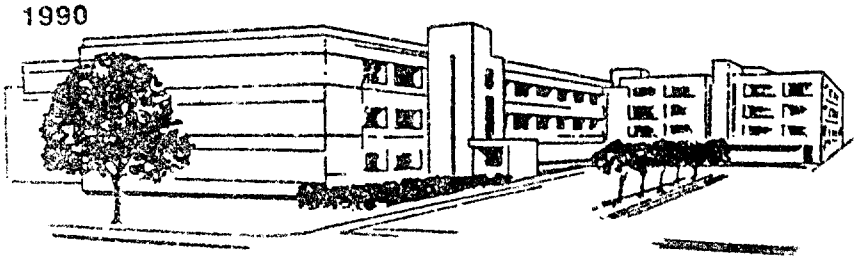
Division of Military Trauma Research

October 1990



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Concentration and Molecular Size Distribution of Dextran in Serum from Rabbits and Dogs Infused with Hypertonic Saline Dextran, M.A. Dubick et al

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Donald G Corby 9 Jan 91

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UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release distribution is unlimited.
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Institute Report No. 456	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Letterman Army Institute of Research 6b. OFFICE SYMBOL (If applicable) SGRD-ULT-M	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Research and Development Command
6c. ADDRESS (City, State, and ZIP Code) Division of Military Trauma Research, LAIR Presidio of San Francisco, CA 94129-6800	7b. ADDRESS (City, State, and ZIP Code) Ft. Detrick, Frederick, MD 21701
8a. NAME OF FUNDING / SPONSORING ORGANIZATION 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code)	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 63807A; PROJECT NO. D836; TASK NO. AX; WORK UNIT ACCESSION NO. 087

11. TITLE (Include Security Classification)
(U) Concentration and Molecular Size Distribution of Dextran in Serum from Rabbits and Dogs Infused with Hypertonic Saline Dextran

12. PERSONAL AUTHOR(S)
M.A. Dubick, J.J. Summary, G.M. Zaucha, J.W. Pfeiffer, D.W. Korte, C.E. Wade

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Institute	FROM _____ TO _____	October 1990	17

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	(U) Dextran-70, rabbits, dogs, hypertonic, resuscitation (U)

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The present study evaluated serum dextran concentration and its molecular size distribution following infusion of 7.5% NaCl/Dextran-70 (HSD) or Dextran-70 alone (D-70) at doses as high as the maximum tolerated dose (MTD). In the first set of experiments beagle dogs were infused i.v. with a single MTD of HSD or D-70 (20ml/kg). At 6h post-infusion, serum dextran concentrations were 15% higher in the D-70 group than the HSD group, but no significant differences were detected at the later times.

In other studies, daily infusion of 2,3, or 4 times a 4 ml/kg dose of HSD or D-70 for 14 d in rabbits resulted in a dose-dependent, progressive rise in plasma dextran concentration. Molecular sizing of dextran in serum at 14 d revealed a shift from 70,000 to 90,000 M.W., reflecting the typical retention of the larger dextran fractions seen following a single bolus infusion. Despite the repeated infusions, molecular size distribution of

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED
22a. NAME OF RESPONSIBLE INDIVIDUAL Donald G. Corby, COL, MC	22b TELEPHONE (Include Area Code) (415) 561-3600 22c. OFFICE SYMBOL SGRD-ULZ

DD Form 1473, JUN 86 *Previous editions are obsolete.* SECURITY CLASSIFICATION OF THIS PAGE

dextran in serum indicated no impairment in excretion of lower molecular weight components. With repeated dosing no significant differences were observed between dextran concentrations following HSD or D-70 infusions. Since serum dextran concentrations reflected the dose infused, the data from these studies suggest that serum dextran concentrations are a useful index of dextran administration and clearance. Despite the high concentrations and loads infused, no adverse effects on any of the animals were detected.

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ABSTRACT

The present study evaluated serum dextran concentration and its molecular size distribution following infusion of 7.5% NaCl/Dextran-70 (HSD) or Dextran-70 alone (D-70) at doses as high as the maximum tolerated dose (MTD). In the first set of experiments beagle dogs were infused i.v. with a single MTD of HSD or D-70 (20ml/kg). At 6h post-infusion, serum dextran concentrations were 15% higher in the D-70 group than the HSD group, but no significant differences were detected at the later times.

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INTRODUCTION

Recent years have seen a renewed interest in the use of dextrans for the treatment of hypovolemia. In particular, a 7.5% NaCl/6% Dextran-70 (HSD) solution has generated numerous experimental studies (1-4) and with reports of potential clinical efficacy in trauma patients (5), HSD is currently undergoing Phase III clinical trials in the U.S.

At present the proposed therapeutic dose of HSD is 4ml/kg or infusion of 250ml to an average 70kg adult. However, others have proposed that 4ml/kg of a 12% Dextran-70 solution may be more efficacious (6) and a smaller dose of 24% Dextran-70 solution has even been proposed (7). However, questions remain regarding the metabolic fate of the infused dextran. Despite the large body of literature on dextran metabolism that has accumulated over the past 40 years (8,9), few studies have addressed the newer Dextran-70 preparations and its narrower molecular weight range, particularly in the presence of hypertonic saline.

Previous investigations with dextrans reported that they were primarily excreted through the kidney (10,11). Glomerular filtration of dextrans with molecular weights > 50-60,000 was very low and dextran was neither reabsorbed nor secreted by the renal tubules (10,12,13). Studies in normal humans have shown that 31-47% of a dose of Dextran-60 or 70 was excreted in urine in the first 24h (10,14,15). Most recently Holcroft, et al. (5) reported that approximately 30% of the dextran remained in plasma 24h following infusion of HSD to trauma victims. In work from our own laboratory, we have observed in experimental animals that the $t_{\frac{1}{2}}$ of dextran in serum was about 7.4 hr in rabbits and 10-12 hr in pigs, following infusion of 4ml/kg HSD (16,17).

The present study monitored dextran metabolism in serum in anticipation of a modified HSD dose or formulation, or expanded uses, such as by multiple dosing. Rabbits and dogs were infused once or daily with doses up to the maximum tolerated dose (MTD) of HSD or Macrodex (Dextran-70 in 0.9% NaCl). Serum concentrations and molecular size distribution of dextran were determined to evaluate the potential for dextran accumulation in the body.

MATERIALS AND METHODS

Animals and Treatment

Dogs: Male (n=4) and female (N=4) beagle dogs, weighing initially 7.5 to 10.9 kg, were obtained from Ridglan Farms, Inc. (Mt. Horeb, WI). They were individually housed in stainless steel runs and fed Purina Canine Diet 5007 and purified water, ad libitum. Dogs were housed in a room controlled for temperature (15.6°-26.7°C) and humidity (10-65%) with a 12 hr photoperiod (0600-1800 hours). All animals were acclimated for at least 12 d before the day of dosing. During this period dogs were quarantined, examined and baseline hematologic and serum chemistry were performed. They were checked daily for signs of illness. For the daily dosing studies, 12 beagle dogs (6 male, 6 female), weighing 8.7-14.4 kg were obtained from Hazelton-LRE (Kalamazoo, MI). Otherwise, animal husbandry conditions were the same.

Rabbits: Male (n=30) and female (n=30) New Zealand White rabbits initially weighing 2.3-3.6 kg were obtained from Hazelton Research Products(Denver, PA). Rabbits were individually housed in stainless steel cages with screen bottoms and fed Purina rabbit chow 5322 and purified water ad libitum. Animals were housed in a room controlled for temperature and humidity as described above for dogs. All animals were checked daily for illness. Water intake was measured daily and body weights were recorded weekly throughout the 14 day study.

Treatment

All animals were randomly assigned to treatment groups. In both dogs and rabbits, preliminary studies were performed to determine the maximum tolerated dose (18,19). In the single dose studies dogs were infused i.v. via the cephalic or saphenous vein with the maximum tolerated dose (MTD) of 20 ml/kg 7.5% NaCl/6% Dextran-70 (HSD) or 6% Dextran-70 (D-70) (AB Pharmacia, Uppsala, Sweden). In the studies where dogs received daily infusions with doses as high as the MTD of HSD or D-70, solutions were administered via surgically implanted femoral vein catheters. Rabbits were also infused daily via surgically implanted femoral vein catheters at doses up to the MTD of HSD or D-70, previously determined to be 16 ml/kg. All infusions were administered over a 5 min period.

In dogs infused with the single dose of HSD or D-70, blood samples were withdrawn prior to and 0.25, 1,2,3,7 and 14 days following infusion. In both rabbit and dog multiple dosing studies, blood samples were withdrawn prior to dosing (baseline) and on days 1,2,3,7 and 14 at a time before the subsequent infusion. Serum was separated from blood cells by centrifugation and stored at -20°C until analyzed.

Dextran Measurements

Total carbohydrate concentrations in serum were determined by the anthrone reaction (20) following precipitation of serum protein with 10% trichloroacetic acid (TCA). Plasma glucose was determined by an automated glucose-hexokinase enzymatic method performed by the Analytical Chemistry Branch, Letterman Army Institute of Research. Plasma dextran concentrations were then estimated by subtracting the glucose concentrations from the concentrations of total carbohydrate. Hematocrit values were determined to monitor the hemodilution effects of HSD and D-70.

Gel Filtration

Serum samples were deproteinized with TCA, neutralized and the protein-free aliquot applied to a 0.9 x 87 cm column of Sephadex 200/100 equilibrated with 0.3% NaCl and eluted with the same solution (21). Fractions were collected and assayed for anthrone-reactive substances as described above. These studies quantitated the molecular weight distribution of the dextran fractions to detect metabolism of dextran following its infusion as HSD or D-70.

Other Assays

Assays for sodium, potassium and chloride were performed by the Analytical Chemistry Branch, Letterman Army Institute of Research. Serum sodium and potassium concentrations were determined with a flame photometer (Instrumentation Laboratory, Lexington, MA). Chloride concentrations were determined by a commercial kit (Roche Diagnostic Systems, Nutley, NJ) for analysis on a Cobas Fara II centrifugal fast analyzer (Roche Analytical Instruments, Belleville, NJ).

Statistical Analysis

Data were statistically analyzed by standard one-way ANOVA with time as the independent variable. At each time period, if a significant F- statistic was obtained, differences between groups were evaluated by Dunnett's or Newman Keuls multiple range test (22). A $p < 0.05$ was considered the level of statistical significance.

RESULTS

Single dose in dogs

The single infusion of HSD or D-70 at the MTD (20 ml/kg) did not affect body weight during the experimental period (data not shown). Water consumption increased nearly 3-fold (2019$\pm$ vs. 699$\pm$208 ml/day) the first day after HSD infusion in comparison to baseline values in this group. No such increase in water consumption was observed in dogs following D-70 infusion. Since these animals were euvolemic, infusion of HSD or D-70 had no significant effect on hematocrits at any of the times assayed (Table 1). During the experimental period D-70 infusion had no significant effect on serum Na, K or Cl concentrations (Table 1). In contrast, 6 hr after HSD infusion, serum Na was significantly higher and K lower, in comparison to baseline concentrations (Table 1). At 24h, the concentrations of these elements were normal and remained so throughout the remaining experimental period. Serum Cl concentrations were not affected by HSD administration.

In dogs infused with a single dose of 20ml/kg HSD or D-70, serum dextran concentrations 6h after infusions were 15% higher in the D-70 than HSD group (Table 2). No significant differences were detected in serum dextran concentrations between groups at all other time points.

Multiple dose in dogs

Daily infusions of HSD or D-70 for 14 days at doses up to 20ml/kg also did not affect body weights. At all doses of HSD, daily water consumption was significantly higher than pre-infusion levels thrcughout the 14 day experimental period whereas water consumption was not affected by daily D-70 infusions (data not shown). In these animals, daily infusion of

HSD and D-70 at the MTD resulted in significantly lower hematocrits in comparison to pre-infusion values (Table 3). In both HSD and D-70 infused dogs, no significant effects on serum Na, K, or Cl concentrations were observed throughout the experimental period (Table 3).

Daily infusion of 12, 16, or 20 ml/kg HSD or D-70 resulted in a dose-dependent, progressive increase in serum dextran concentrations (Fig 1). In general dextran concentrations were similar in the dogs infused with 16 or 20 ml/kg and these concentrations were significantly higher than those measured in dogs infused with 12ml/kg. In addition, at each dose level, serum dextran concentrations on comparable days were slightly lower in dogs infused with HSD than D-70, but the differences were not statistically significant.

Multiple dosing in rabbits

Daily infusion of the MTD (16ml/kg) of HSD or D-70 for 14 days in rabbits also did not affect body weights throughout the experimental period. In contrast to dogs, daily infusion of the compounds also did not significantly affect water consumption (data not shown).

In the D-70 group, hematocrits were significantly lower than pre-infusion levels from day 2 to the end of the experimental period, whereas in the HSD group, hematocrits were significantly lower than pre-infusion values from day 3 to 14 (Table 3). In both groups, serum Na, K and Cl were not significantly affected by D-70 or HSD infusion at any of the times assayed (Table 3).

In rabbits infused daily with 8, 12 or 16ml/kg of HSD or D-70, a progressive dose-response increase in serum dextran concentrations was also observed over the 14-day experimental period (Fig 2). As observed in the dog studies, no significant differences in serum dextran concertrations were detected following infusion of the 12 or 16ml/kg dose, and these concertrations were higher than those observed following infusion of 8ml/kg. In addition, at each time period assayed, no significant differences were observed in serum dextran concentrations between animals receiving the same dose of HSD or D-70. Gel filtration chromatography of serum from rabbits infused daily with the MTD of 16 ml/kg showed the typical shift to the left, corresponding to a shift in peak molecular weights from 70,00 to 90,000 for both HSD and D-70 over the 14 day period (Fig 3). Despite the multiple infusions, there appeared to be no

decrement in the serum clearance of low molecular weight dextran components.

Discussion

Current experimentation with hypertonic/hyperoncotic solutions, e.g., HSD, for the treatment of hypovolemic states has led to 4 ml/kg as the recommended therapeutic dose (cf 16). More recently, others have begun experimenting with higher dextran or salt concentrations to derive a greater cardiodynamic benefit (6,7). As these studies have progressed, it has become clear that a better understanding of dextran metabolism, at varying NaCl and Dextran-70 loads, could help design more rational therapeutic approaches and avoid potentially adverse effects.

In the present study, 6h following infusion of a single bolus of the maximum tolerated dose of 20 ml/kg of HSD to euvolemic dogs, serum Na and K concentrations were significantly different than pre-infusion levels although peak concentrations were not determined. At 24h, Na and K concentration had returned to normal. This is in agreement with previous studies that have shown a peak rise in serum Na within minutes after an infusion of HSD or hypertonic saline, then a slow return of serum Na toward normal levels (2, 23-25). This return to baseline occurs more rapidly if the animals are allowed free access to water following HSD infusion, and under these conditions Na concentrations are normal by 24h post-infusion (23). Since animals in the present study were allowed free access to water, it is not surprising that serum Na concentrations are normal 24h after HSD infusion and that Na metabolism was not altered following daily HSD infusions for 14 d in either rabbits or dogs.

In addition, the decrease in serum K observed in dogs 6h following a single MTD of HSD was transient and was not clinically significant. Daily infusions of HSD or D-70 also did not affect serum K concentrations in rabbits or dogs. Serum Cl concentrations were not affected in either species during the 14 day experimental period.

At the 6h time point in the single-dose study, serum dextran concentrations were approximately 15% higher in dogs infused with Dextran-70 (D-70) than HSD. It was possible that this difference reflected a greater hemodilution induced by HSD than D-70, but this was not supported by the hematocrit values obtained.

Although body weights were not statistically different between the groups, the D-70 group consistently weighed a little more, so these initial differences may reflect the D-70 group as a whole receiving more dextran than the HSD group. In general, this serum dextran concentration was 3-4 times higher than the 6h concentration observed in normal rabbits or pigs infused with 4 ml/kg HSD (16,17). Nevertheless, at the subsequent times, dextran concentrations were nearly identical in both groups for the remainder of the experimental period. In both the HSD and D-70 dogs, serum dextran concentrations were essentially undetectable 72h after infusion. In previous studies with rabbits and pigs infused with 4 ml/kg HSD, we observed serum $t_{\frac{1}{2}}$'s of 7.4 and 10-12 hr, respectively (16,17). Thus, the data from the present studies are consistent with these observations and suggest that although the dogs were infused with 5 times the dose of HSD or D-70 used previously, the rate of dextran clearance from serum did not appear to be altered.

In the second set of experiments, rabbits and dogs were infused daily for 14 d, i.v., with multiples of the 4 ml/kg dose, to their respective MTD. In preliminary studies this was determined to be 16 ml/kg for rabbits (19). Serum dextran concentrations were measured to see if dextran accumulation correlated with any observed toxicity. Based on the serum $t_{\frac{1}{2}}$ of dextran previously observed in rabbits (17), 24h was not long enough to totally clear a 4 ml/kg dextran dose from serum, so its accumulation was expected. A dose-response increase in serum dextran concentrations was observed in both HSD and D-70- infused rabbits. In both HSD and D-70-infused rabbits, at all doses, serum dextran concentrations were observed to increase about 4 to 6 times the corresponding concentrations determined on day 1.

This increase in dextran serum concentrations does not suggest a change in the rate of its serum clearance, despite daily infusion at the MTD. Further analysis of serum dextran in rabbits infused with 16ml/kg HSD and D-70 revealed a shift in higher molecular weight fractions from 70,000 to 90,000 over the 14 day period. This shift is consistent with previous reports following a single "therapeutic" dose of D-70 or HSD (26,17). The relatively small magnitude of the shift observed in the present study suggests that renal clearance of dextran was not significantly affected by daily infusion of such large doses. However, urine was not available in this study to confirm this hypothesis.

In conclusion, these data indicate that daily infusion of HSD or D-70, at doses as high as the maximal tolerated dose to rabbits and dogs resulted in serum dextran concentrations as high as 2500 mg/dl. In addition the serum concentrations generally reflected the dose infused. Despite such high concentrations (up to five times those previously observed in the treatment of hypovolemia (16,17)), no overt toxicity or altered dextran clearance was observed. In addition, serum Na, Cl and K levels were also maintained within acceptable limits, even following daily infusions at the MTD. Since the current proposed therapeutic dose of HSD is a single 4ml/kg dose, the present study indicates that few adverse effects would be encountered, even if the dose was doubled or multiple infusions given.

REFERENCES

1. Kramer GC, English TP, Gunther RA, Holcroft JW:Physiological mechanisms of fluid resuscitation with hyperostotic/hyperoncotic solutions. In: Passmore JC, Reichard SM, Reynolds DG, Taber DL, eds. "Perspectives in Shock Research: Metabolism, Immunology, Mediators and Models". New York: Alan R. Liss, Inc. 1989; 311-320.

2. Hands R, Holcroft JW, Perron PR, Kramer GC: Comparison of peripheral and central infusion of 7.5% NaCl/6% dextran 70. Surgery 1988; 103:684-689.

3. Chudnofsky CR, Dronen SC, Syverud SA, Zink BJ, Hedges JR: Intravenous fluid therapy in the prehospital management of hemorrhagic shock: Improved outcome with hypertonic saline/6% Dextran-70 in a swine model. Am J Emerg Med 1989; 7:357-363.

4. Maningas PA: Resuscitation with 7.5% NaCl in 6% dextran-70 during hemorrhagic shock in swine: Effects on organ blood flow. Crit Care Med 1987; 15:1121-1126.

5. Holcroft JW, Vassar MJ, Perry CA, Gannaway WL, Kramer GC: Perspectives on clinical trials for hypertonic saline/dextran solutions for the treatment of traumatic shock. Brazilian J Med Biol Res 1989; 22:291-293.

6. Halvorsen L, Gunther RA, Holcroft JW: Dose response characteristics of hypertonic saline dextran solutions, Eur Surg Res, 1990, in press.

7. Pascual JMS, Watson JC, Runyon DE, Clifford CB, Kramer GC: Sodium and fluid loads during resuscitation of hemorrhagic shock using isotonic and hypertonic saline dextran solutions. Circ Shock 1990; 31:68.

8. Gruber UF: Blood Replacement. Berlin: Springer-Verlag, 1969.

9. Hunt H: Relationships between the chemical and physicochemical properties of dextran and its physicochemical effects. In: Derrick JR, Guest MM, Charles CE, Thomas C, eds. Dextran Current Concepts of Basic Actions and Clinical Applications. Springfield, IL: Charles C. Thomas Publishers. 1971; 3-26.

10. Arturson G, Wallenius G: The renal clearance of dextran of different molecular sizes in normal humans. Scand J Clin Lab Invest 1964; 1:81-86.

11. Arturson G, Granath K, Thoren L, Wallenius G: The renal excretion of low molecular weight dextran. Acta Chir Scand 1964; 127:543-551.

12. Arturson G, Granath K, Grotte G: Intravascular persistence and renal clearance of dextran of different molecular sizes in normal children. Arch Dis Child 1966; 41:168-171.

13. Leypoldt JK, Frigon RP, DeVore KW, Henderson LW: A rapid renal clearance methodology for dextran. Kidney Internat 1987; 31:855-860.

14. Harrison JH: Dextran as a plasma substitute with plasma volume and excretion studies on control patients. Ann Surg 1954; 139:137-142.

15. Thoren L: The dextrans-Clinical data. Develop Biol Standard 1980; 48:157-167.

16. Dubick MA, Summary JJ, Ryan BA, Wade CE: Dextran concentrations in plasma and urine following administration of 6% Dextran-70/7.5% Na Cl to hemorrhaged and euvolemic conscious swine. Circ Shock 1989; 29:301-310.

17. Dubick MA, Summary JJ, Wade CE: Plasma Clearance and tissue distribution of dextran following infusion of hypertonic saline/dextran to euvolemic and hemorrhaged rabbits. Circ Shock 1990; 31: 66.

18. Zaucha GM, Frost DF, Omaye ST, Clifford CB, Korte DW Jr: Fourteen day subacute intravenous toxicity study of hypertonic saline/Dextran-70 and its constituents in beagle dogs. Letterman Army Institute of Research Institute Report #404, November 1989.

19. Zaucha GM, Frost DF, Omage ST, McKinney LA, Peare MJ, Korte DW Jr: Fourteen-day subacute intravenous toxicity study of hypertonic saline/Dextran-70 and its constituents in New Zealand White rabbits. Letterman Army Institute of Research Report #405, November, 1989.

20. Roe JH: The determination of dextran in blood and urine with anthrone reagent. J Biol Chem 1954; 208:889-896.

21. Nilsson G, Nilsson K: Molecular weight distribution determination of clinical dextran by gel permeation chromatography. J Chromatogr 1974; 101:137-153.

22. Remington RD, Schork MA: Statistics with Applications to the Biological and Health Sciences. Englewood Cliffs: Prentice Hall Inc., 1970.

23. Maningas PA, DeGuzman LR, Tillman FJ, Hinson CS,Priegnitz KJ, Volk KA, Bellamy RF. Small-volume infusion of 7.5% NaCl in 6% Dextran 70 for the treatment of severe hemorrhagic shock in swine. Ann Emerg Med 1986; 15 (10): 1131-1137.

24. Velasco IT, Pontierri V, Rocha e Silva M. Hyperosmotic NaCl and severe hemcrrhagic shock. Am J Physiol 1980; 239: H664-H673.

25. Wade CE, Hannon JP, Bossone CA, Hunt MM, Loveday JA, Coppes R, Gildengorin VL. Resuscitation of conscious pigs following hemorrhage: Comparative efficacy of small-volume resuscitation. Circ Shock 1989; 29: 193-204.

26. Arturson G: The change of molecular weight distribution of infused dextran, Scand J Clin Lab Invest 1965; 17(Suppl 86): 69-79.

Acknowledgement

The authors thank Jacqueline Y. Green for technical assistance and Mr. Donald L. Calkins for preparation of the manuscript.

Table 1
Hematocrits and Serum Na, K, Cl in Dogs Infused with 20ml/kg of HSD or D-70.

		DAY						
		0	0.25	1	2	3	7	14
Hct (%)	HSD	45±2	44±1	44±2	45±2	45±1	44±2	45±2
	D-70	45±2	45±2	44±2	46±3	46±1	46±4	46±2
Na (Meq/l)	HSD	152±2	157±1*	152±1	152±1	152±3	151±1	145±2
	D-70	152±2	151±2	152±2	152±2	151±1	149±1	150±1
K (Meq/l)	HSD	5.2±0.1	4.1±0.1*	4.7±0.1	4.9±0.1	5.0±0.2	5.2±0.2	4.8±0.2
	D-70	5.1±0.2	5.1±0.1	4.8±0.2	4.9±0.2	4.8±0.2	4.8±0.2	4.8±0.2
Cl (Meq/l)	HSD	110±1	116±2	112±1	110±2	113±2	112±1	109±4
	D-70	113±1	114±1	113±1	111±1	113±1	114±1	113±1

[1]Data expressed as mean ± S.E. from 4 dogs/group
*p<0.05 from time 0 value.

Table 2

Serum Dextran Concentrations in Dogs Infused with 20ml/kg of HSD or Dextran-70

DAY	HSD (n=4)	D-70 (n=4)
0.25	864±29	991±34*
1	671±64	674±43
2	261±60	333±47
3	132±12	154±15
7	ND[2]	ND
14	ND	ND

1Data expressed as mean ±S.E. of mg/dl.
[2]ND- not detectable
*$p<0.05$ from HSD group

Table 3

Hematocrits and Serum Na, K, Cl Concentrations in Dogs and Rabbits Infused Daily with HSD or D-70

			0	1	2	3	7	14
Dogs (nz6) (Daily Infusion of 20ml/kg)	HCT (%)	HSD	50±1	45±1*	46±1	44±1*	42±1*	42±3*
		D-70	48±1	46±1	44±1*	42±1*	38±1*	37±1*
	Na (Meq/l)	HSD	153±1	156±2	152±1	151±1	152±1	151±1
		D-70	154±1	155±2	154±2	148±4	152±1	150±1
	K (Meq/l)	HSD	4.9±0.2	4.7±0.1	4.6±0.1	4.8±0.1	4.4±0.1	4.6±0.1
		D-70	4.9±0.1	4.7±0.1	4.7±0.1	4.6±0.2	4.4±0.1	4.6±0.1
	Cl (Meq/l)	HSD	114±1	120±2	117±1	116±1	117±1	118±1
		D-70	116±1	118±1	119±1	117±1	119±1	118±1
Rabbits (n=10) (Daily Infusion of 16ml/kg)	HCT (%)	HSD	33±1	31±1	29±1	27±1*	25±1*	24±1*
		D-70	34±1	31±1	28±1*	27±1*	26±1*	25±1*
	Na (Meq/l)	HSD	150±2	150±1	148±1	149±1	147±1	146±1
		D-70	150±1	149±1	148±1	148±1	146±1	147±1
	K (Meq/l)	HSD	4.1±0.1	4.2±0.2	4.3±0.1	4.2±0.1	4.1±0.1	4.5±0.2
		D-70	3.8±0.1	4.0±0.1	4.0±0.2	4.2±0.1	4.2±0.2	4.1±0.2
	Cl (Meq/l)	HSD	112±1	112±1	114±1	114±1	112±1	112±1
		D-70	115±1	114±1	114±1	114±1	113±1	114±1

Data expressed as mean ±SE
* $p < 0.05$ from time 0 value

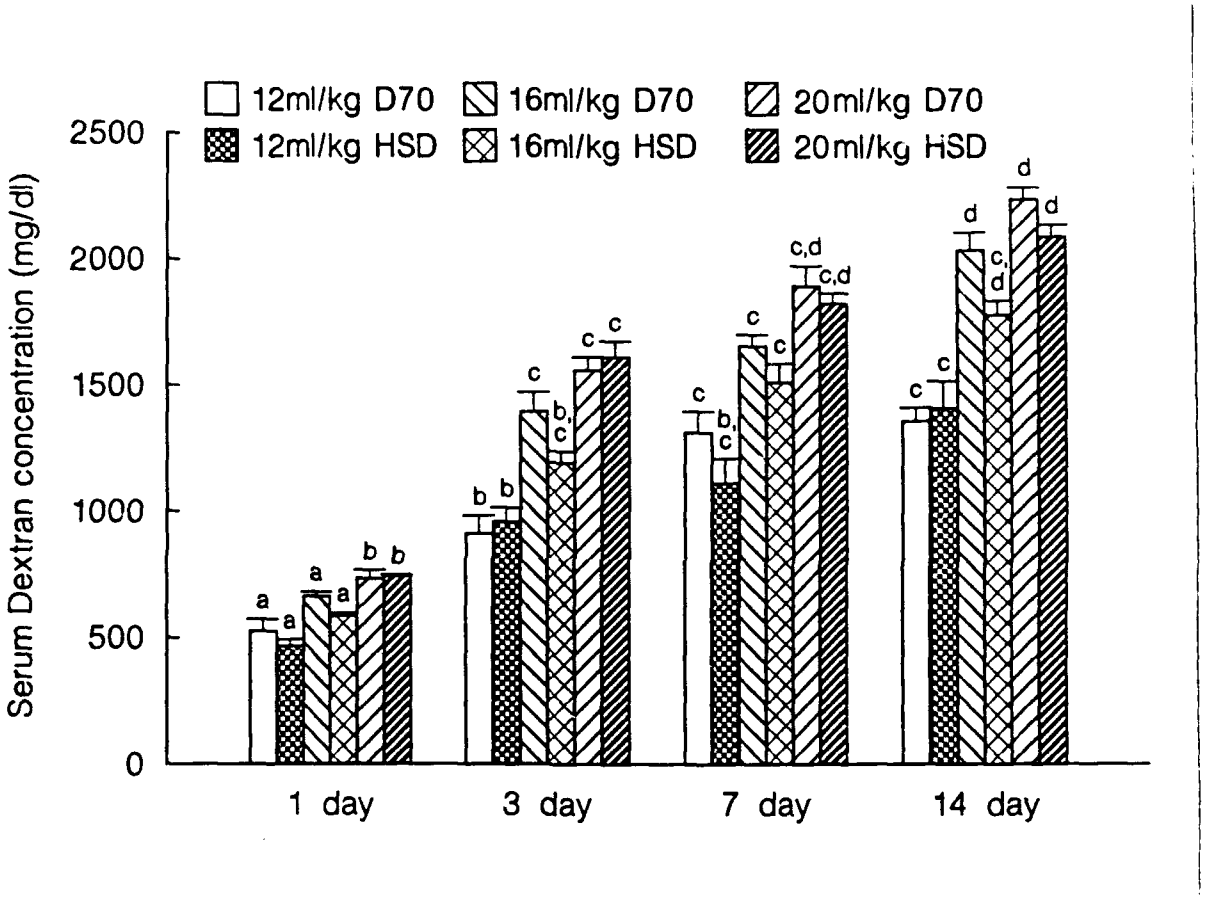

Fig 1. **Serum dextran concentrations in euvolemic dogs infused daily with 12, 16, or 20 ml/kg HSD or D-70. Data represents mean ±S.E. of 4 animals at each time point. Different superscript denotes significant difference ($p<0.05$).**

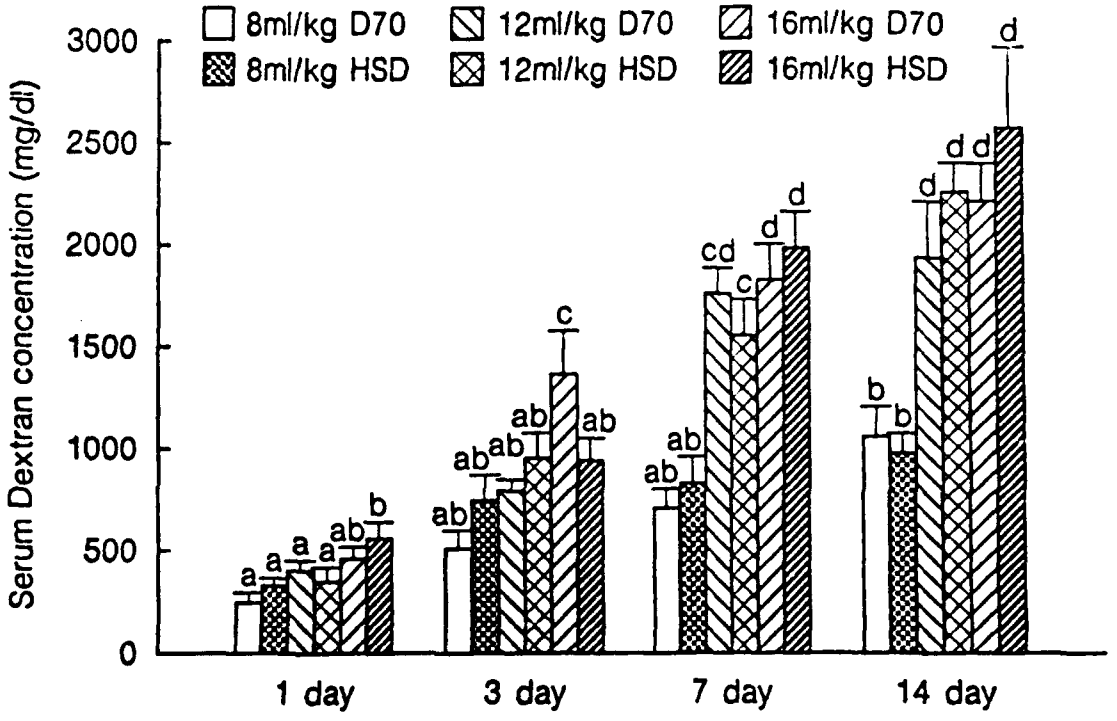

Fig 2. **Serum dextran concentration in euvolemic rabbits infused daily with 8,12 or 16 ml/kg HSD or D-70. Data represent mean ±S.E. of 4-6 determinations at each time point. Different superscript denotes significant difference ($p<0.05$).**

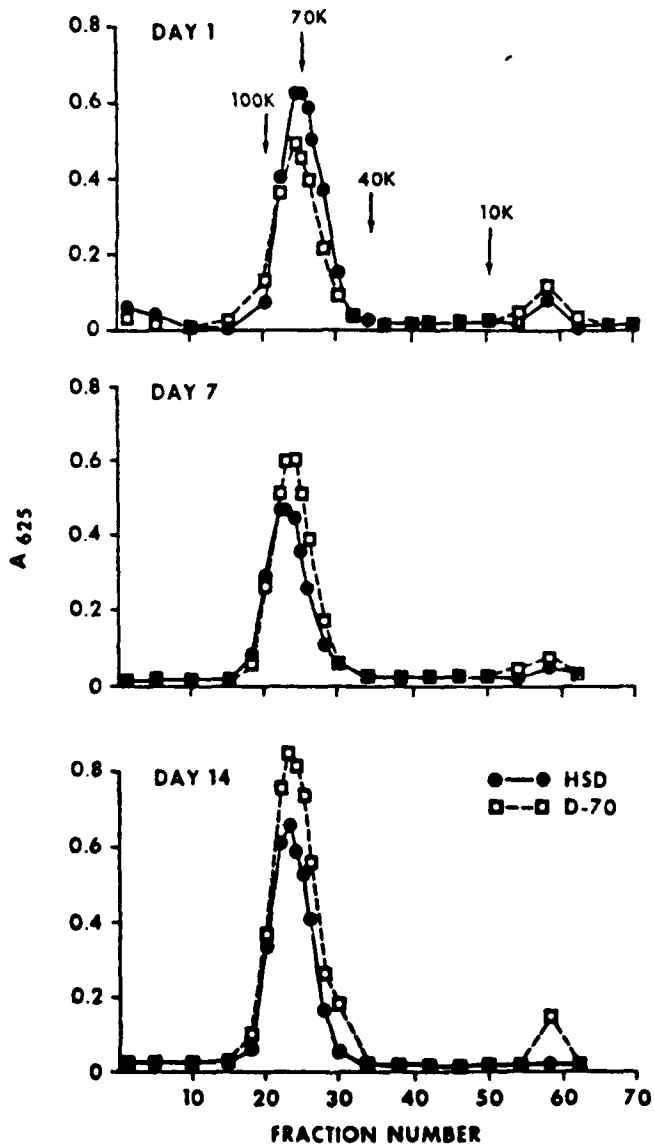

Fig 3. Molecular weight distribution of dextran in serum from rabbits infused daily with 16ml/kg of HSD (closed circles) or Dextran-70 (open squares).

Legend To Figures

Fig 1. Serum dextran concentrations in euvolemic dogs infused daily with 12, 16, or 20 ml/kg HSD or D-70. Data represents mean ±S.E. of 4 animals at each time point. Different superscript denotes significant difference ($p<0.05$).

Fig 2. Serum dextran concentration in euvolemic rabbits infused daily with 8,12 or 16 ml/kg HSD or D-70. Data represent mean ±S.E. of 4-6 determinations at each time point. Different superscript denotes significant difference ($p<0.05$).

Fig 3. Molecular weight distribution of dextran in serum from rabbits infused daily with 16ml/kg of HSD (closed circles) or Dextran-70 (open squares).

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