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THE EFFECTS OF DEXTRAN IN NORMOVOLIC AND OLIGEMIC SUBJECTS¹

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Dextran, a macromolecular plasma volume expander, was first used in 1943. Since that time, many clinical reports have appeared in the Scandinavian and English literature. In 1942 the Blood Substitute Committee of the National Research Council listed 11 requirements for a satisfactory plasma volume extender. These are: maintenance of satisfactory colloid osmotic pressure, constant composition, suitable viscosity, stability with temperature change, stability in storage, ease of sterilization, freedom from pyrogens, absence of immediate adverse effects, absence of immediate or delayed organic derangement, absence of antigenicity, and reasonable price (1). Dextran seems to fulfill all of these requirements except for the possible possession of antigenic properties. In addition, it has been suggested that a satisfactory extender should remain in the circulatory system, maintain increased plasma volume, and keep blood circulatory levels up to 50 per cent of the amount infused for at least 12 hours (1). Although it is of paramount importance that effects of any plasma volume expander upon plasma volume and plasma protein restitution be investigated, there has been a paucity of such reports in the literature.

METHODS

The experimental procedure was divided into two parts. In the first part, after control studies were performed, one liter of 6 per cent dextran² in saline was administered

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² Clinical dextran, lot No. 84667A, Commercial Solvents Corporation, was administered to six patients. Four patients received clinical dextran prepared at the Northern Regional Research Laboratory, Peoria, Illinois from Strain NRRL-B-742. Since the effects of these two forms of dextran did not differ significantly, they have been considered collectively in the tabulation of results.

All of the subjects who were bled received clinical dex-

travenously in 50 minutes to 10 male patients convalescent from various diseases. The patients had no evidence of cardiovascular or renal disease and varied in age from 19 to 37 years. The plasma volume was measured one and six hours after the administration of dextran. The hematocrit, plasma protein concentration, plasma dextran concentration, and urinary dextran excretion were measured at 1, 6, and 24 hours.

The second part of the experiment consisted of the investigation of the effects of dextran after hemorrhage. The subjects were eight healthy male physicians varying in age from 25 to 32 years. After the control studies were performed, one liter of blood was removed from the antecubital vein in 15 minutes. Immediately thereafter, one liter of 6 per cent dextran in saline was administered intravenously during a 40 minute period. The plasma volume was measured at 6 and 24 hours in all subjects, at 1 hour in five subjects and at 12 hours in three subjects. The hematocrit, plasma protein concentration and plasma dextran concentration were determined at 1, 6, 24, and 48 hours in all subjects and at 12 hours in three subjects. The urinary dextran excretion was determined at 1, 6, and 24 hours in all subjects and at 12 hours in three subjects.

The plasma volume was measured by the T-1824 dye method as previously reported (2). Samples were drawn at five minute intervals from 10 to 35 minutes after dye administration. The red cell volume was calculated from the total blood volume and plasma volume. The total blood volume was calculated from the plasma volume and the hematocrit which was corrected for 4 per cent trapped plasma. Plasma protein concentration in the subjects who were bled was determined by the micro-Kjeldahl method. In the other group plasma protein concentration was determined by the tyrosine method (3) and frequently checked by the micro-Kjeldahl method. Protein could not be determined by the biuret method since dextran is precipitated by copper in an alkaline medium. Dextran was determined by the method of Bloom and Wilcox (4).

RESULTS

The administration of dextran produced a very slight elevation of blood pressure in most subjects. There were no changes in pulse or temperature. Dextran, lot No. 84667A, Commercial Solvents Corporation.

TABLE I
Effects of administration of 1 liter of dextran *

	Time in hours		
	1	6	24
Increase in plasma volume (ml.)	775 ± 150	534 ± 117	
Decrease in hematocrit (%)	12.4 ± 2.1	8.6 ± 2.1	5.3 ± 2.6
Change in red cell volume (ml.)	-9 ± 168	33 ± 132	
Decrease in plasma protein concentration (%)	21.7 ± 2.5	12.7 ± 2.7	5.3 ± 4.7
Change in total circulating protein (grams)	-2.1 ± 10.6	6.9 ± 13.6	
Plasma dextran concentration (mg. per 100 ml.)	1,072 ± 94	684 ± 75	416 ± 36
Total circulating dextran (grams)	39.4 ± 2.5	23.4 ± 1.7	
Cumulative urinary dextran excretion (grams)	13.6 ± 2.5	22.5 ± 4.3	28.6 ± 6.0
Dextran unaccounted for (grams)	7.0 ± 3.9	15.1 ± 4.9	

* All values are expressed as the mean and standard deviation.

ature. The removal of one liter of blood was not associated with any change in pulse and was associated with symptoms in only one subject. This subject developed transient faintness, nausea, and tingling in the hands and feet. Following the completion of the experiment, one subject developed headache, fever, anorexia, diarrhea, and splenomegaly. The illness was of 10 days' duration. Extensive clinical and laboratory investigation failed to reveal a specific diagnosis.

The effects of the administration of one liter of dextran to patients with a normal blood volume are given in Table I. The plasma volume increased 775 ml. at one hour. At six hours the increase was 534 ml. There was a corresponding decrease in plasma dextran concentration from 1,072 to 684 mg. per 100 ml. during this time. The urinary dextran excretion was 22.6 per cent of the injected dose (60 grams) in one hour. An additional 15 per cent was excreted from one to six hours.

There was no statistically significant change in the total circulating proteins and the red cell volume. From the increase in plasma volume and from the values for total circulating dextran it was calculated that there was a retention of 21.2 ml. of water per gram of dextran.

The effects of the administration of one liter of dextran following the removal of one liter of blood are given in Table II. The increases in plasma volume were determined using the plasma volume immediately after venesection as the baseline. The plasma volume immediately after venesection was calculated by subtracting the amount of plasma removed from the control plasma volume. The changes in plasma volume thereafter are illustrated graphically in Figure 1. There was an increase in plasma volume of approximately one liter in one hour. The plasma dextran concentration was 1,160 mg. per 100 ml. in one hour and fell progressively to 247 mg. per 100 ml. in 48 hours.

TABLE II
Effects of administration of 1 liter of dextran following removal of 1 liter of blood *

	Time in hours				
	1	6	12	24	48
Increase in plasma volume (ml.)	1,020 ± 115	820 ± 179	700 ± 197	860 ± 269	
Decrease in hematocrit (%)	20.9 ± 2.6	16.6 ± 2.1	16.2 ± 3.4	16.9 ± 3.1	19.7 ± 2.7
Change in red cell volume (ml.)	-58 ± 160	23 ± 173	12 ± 65	28 ± 154	
Decrease in plasma protein concentration (%)	26.1 ± 3.3	18.0 ± 3.0	14.6 ± 0.5	13.1 ± 2.7	11.4 ± 3.0
Protein added to circulation after bleeding (grams)	3.3 ± 3.6	15.7 ± 9.0	19.2 ± 11.3	30.6 ± 13.7	
Plasma dextran concentration (mg. per 100 ml.)	1,160 ± 117	726 ± 91	644 ± 47	431 ± 62	247 ± 24
Total circulating dextran (grams)	41.5 ± 1.8	24.9 ± 2.0	19.8 ± 2.2	14.9 ± 1.5	
Cumulative urinary dextran excretion (grams)	15.9 ± 2.0	27.6 ± 3.0	33.3 ± 1.8	35.0 ± 3.8	
Dextran unaccounted for (grams)	2.6 ± 3.2	7.5 ± 3.8	6.9 ± 1.0	10.1 ± 4.2	

* All values are expressed as the mean and standard deviation.

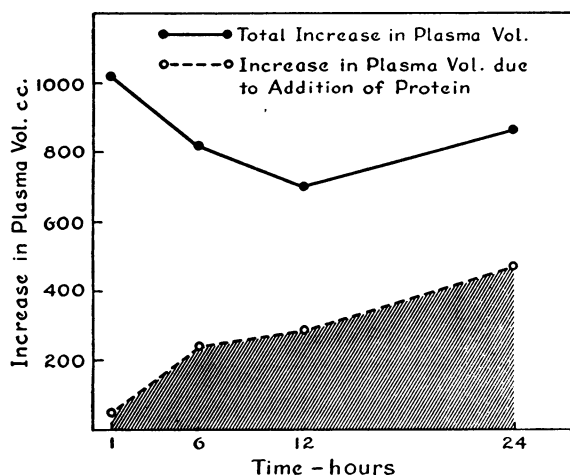


FIG. 1. INCREASE IN PLASMA VOLUME FOLLOWING DEXTRAN ADMINISTRATION TO OLIGEMIC SUBJECTS

The shaded area represents the increase in plasma due to the addition of protein to the circulation.

The urinary dextran excretion in one hour was 26.4 per cent of the injected amount. An additional 19.4 per cent was excreted from one to six hours and 12.4 per cent in 6 to 24 hours. The amount of dextran that could not be accounted for in the plasma and urine increased from 2.6 grams in one hour to 10.1 grams at 24 hours. This is noted graphically in Figure 2. The addition of plasma protein to the circulation increased from 3.3 grams during the first hour after the dextran infusion to 30.6 grams at 24 hours. There was no significant change in red cell volume during the time of the experiment.

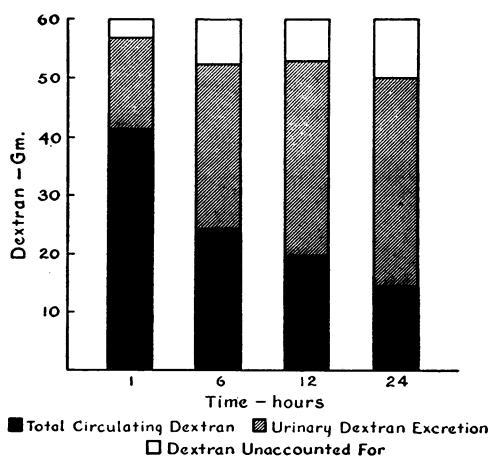


FIG. 2. TOTAL CIRCULATING DEXTRAN, URINARY DEXTRAN EXCRETION, AND DEXTRAN UNACCOUNTED FOR IN SUBJECTS WHO WERE BLEED

DISCUSSION

From the results presented it is apparent that dextran is effective in increasing plasma volume in both the normovolemic subjects and in subjects who were bled. The plasma dextran concentration and the urinary excretion of dextran were similar in the two groups. The important question has been raised as to whether the normovolemic or the hypovolemic patient or animal should be used for the evaluation of plasma expanders (5). Some investigators believe that homeostatic mechanisms may correct a supernormal volume rapidly and that more of the infused material will be excreted in the urine (5, 6). This was not borne out in our experiments. It is not intended to imply, however, that the renal excretion of dextran would be similar in subjects with greater blood loss.

During the various experimental periods, some of the administered dextran was unaccounted for by addition of the total circulating dextran and urinary dextran excretion (Figure 2). This experiment provides no specific information as to the fate of this portion. It is assumed that a considerable fraction of the dextran which is unaccounted for is present extravascularly during the early part of the experiment and that some may be metabolized. It has been previously demonstrated that dextran appears rapidly in lymph (7). Experiments utilizing C^{14} tagged dextran showed that over 90 per cent of a dose of dextran was eliminated in 10 days. Sixty-four per cent appeared in the urine and 26 per cent in the expired air as carbon dioxide (8). The excretion of dextran as carbon dioxide began almost immediately and reached a peak on the second to third day. There is also evidence that dextran is metabolized to glucose (9).

Following hemorrhage the administration of dextran was associated with an increase in plasma volume, which was sustained for 24 hours. The increase at 24 hours was 860 ml. This is in contrast to the normovolemic subjects in whom the increase in plasma volume was only 534 ml. at six hours. A further decrease in plasma volume of this group occurred at 24 hours as evidenced by the hematocrit. The difference between the two groups is not related to the amount of circulating dextran but rather to the addition of significant amounts of protein to the circulation, in the bled

subjects. Hemodilution due to such addition of protein becomes progressively more important as is graphically illustrated by the shaded area in Figure 1. At 1, 6, and 24 hours there were 3.3, 15.7, and 30.6 grams of plasma protein, respectively, added to the circulation of subjects who were bled. This is comparable to the values reported by Ebert, Stead, and Gibson (10) in a bleeding experiment in which no plasma volume expander was administered. It is therefore apparent that dextran has no inhibitory effect on the innate ability of an oligemic subject to add protein to the circulation and to restore the blood volume to normal.

It has been suggested by Rosenqvist and Thorsen (11) that dextran lowers the concentration of plasma proteins by dilution and also by supplanting plasma proteins, particularly albumin. If it were true that dextran inhibited the addition of protein to the circulation, then the plasma volume in the oligemic subjects would have declined rapidly. The rapid urinary excretion of dextran, unassociated with the natural process of hemodilution, would not have permitted a sustained increase in plasma volume. Our studies do not confirm the observations of Rosenqvist and Thorsen.

Kinard and Bloom (6) and Bohmansson and his coworkers (12) have suggested that the administration of dextran will cause the addition of red blood cells to the active circulation. Our data indicate that there was no appreciable early addition of red cells to the circulation in response to dextran nor in response to hemorrhage followed by the administration of dextran. The greater decrease in protein concentration as compared to the hematocrit is to be expected since the per cent increase in plasma volume is greater than the per cent increase in the total blood volume. The apparent discrepancy in change of the protein concentration and the hematocrit should not be construed as indicating the addition of red cells to the circulation.

The total circulating dextran at 12 hours was 33 per cent of the amount injected. This does not satisfy the proposed requirement that the circulatory level should be maintained at 50 per cent for 12 hours (1). It is noteworthy, however, that despite the decrease in plasma dextran concentration, the plasma volume remained relatively

stable. Dextran has a colloid osmotic pressure approximately that of plasma. Hence, a better criterion for adequate retention of dextran in the plasma would be a degree of retention sufficient to insure that the sum of the circulating dextran and the protein added to the circulation remains relatively constant at a value sufficient to sustain a satisfactory increase in plasma volume. In these experiments this sum was 45, 41, 39, and 46 grams at 1, 6, 12 and 24 hours, respectively. Bull and associates (13) have indicated this in another manner by stating that "the main function of the substitute would clearly be to restore circulating blood volume until the patient's own plasma protein returned to the circulation." Since dextran fulfills this criterion, it must be considered as a satisfactory plasma volume expander.

SUMMARY

Dextran was administered to subjects with a normal blood volume and to subjects with oligemia induced by the rapid removal of one liter of blood. The effect of dextran in expanding the plasma volume was more prolonged in those subjects who were bled. This is accounted for by the addition of plasma protein to the circulation. The importance of the restitution of plasma proteins in the evaluation of any plasma volume expander is discussed.

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