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Dextran Infusions and Extracellular Volume[1,2]

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The administration of dextran results in a lowered albumin pool, mainly due to a decrease in the amount of albumin located intravascularly (1). Upon the addition of cortisone these changes in albumin distribution are reversed (1). Also while dextran produces an increase in the plasma volume (2), data concerning the effects of dextran on the extracellular fluid are not available. These shifts in the distribution of albumin might be associated with changes in total extracellular volume and interstitial volume. The present report describes the measurement of the plasma volume, the extracellular sucrose space, and albumin distribution in rabbits treated with dextran and dextran and cortisone.

METHODS

All studies were performed in female rabbits weighing 1.9-4.0 kg. Dextran[3] (av mol wt 188,000) was administered intravenously in doses of 1.0-1.5 gm per day as a 6 per cent solution in physiological saline.[4] Cortisone acetate (3 mg/kg/day) was injected subcutaneously. All rabbits receiving cortisone were given 25 mg streptomycin and 25,000 units of penicillin every other day to guard against infection. The drinking water contained KCl supplements of which the rabbits consumed 2-3 meq per day.

The plasma volume and extracellular volume were determined in 16 control rabbits and in 15 rabbits treated with dextran for 11-19 days and in five rabbits treated first with dextran for 12-19 days and then cortisone for an additional eight

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[3]Obtained from Pharmechem Corp., Bethlehem, Pa. Molecular wt. determined by light scattering according to the method of Doty and Steiner (3).

[4]Each animal was given dextran until it achieved a steady state with respect to serum albumin concentration. Since each animal required a different length of time on dextran to achieve this new steady state, the grouping together of these data is valid on the grounds that the animals were all in the same experimental state when the measurements were carried out.

through ten days. The extracellular volume was determined from the space of distribution of ^{14}C sucrose[1] employing the single injection extrapolation method (4). Following the intravenous administration of 20-40 μC of ^{14}C sucrose into an ear vein, heparinized bloods were obtained from the opposite ear at 20, 40, and 60 minutes. Following the 60 minute blood sample 1-2 μC of rabbit albumin ^{131}I were injected and blood samples obtained six and ten minutes later for the measurement of the plasma volume (1).

Plasma samples were assayed for ^{14}C in a flow gas counter. All samples were assayed in triplicate with 0, 0.1, 0.2, and 0.3 ml carrier free ^{14}C sucrose in distilled water to correct for internal absorption (5,6). ^{131}I was assayed in a well type scintillation counter.

The last two plasma samples contained both isotopes. The total counting rate in the flow gas counter was corrected for the activity contributed by the ^{131}I. This amounted to about 25 per cent of the ^{14}C activity. The concentration of ^{14}C (cpm/ml) was plotted on semilogarithmic paper as a function of time, and the intercept of the linear portion of the curve extrapolated to zero time was used to calculate the extracellular volume (Fig. 1). No correction for plasma protein concentration was applied. Essentially the complete dose of ^{14}C sucrose could be accounted for in the urine or still circulating in the original calculated extracellular space 1-1.5 hours following the injection. At that time no ^{14}C activity was found in the gall bladder bile. No evidence for red cell penetration or metabolism of ^{14}C sucrose in whole blood could be obtained after incubation of ^{14}C sucrose with whole rabbit blood. The use of the single injection extrapolation method for the measurement of extracellular space has been criticized be-

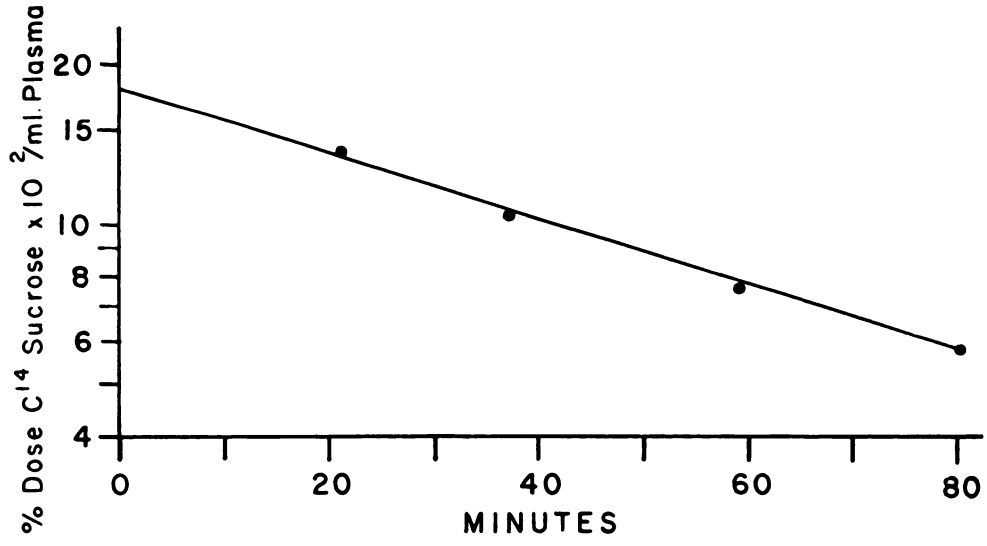

Fig. 1. Extracellular Space. Typical rabbit study. Plasma disappearance curve following the intravenous injection of sucrose-U-^{14}C. (See Text).

[1]Obtained from Picker Laboratories, White Plains, New York.

cause of the doubt that equilibration ever occurs, and if it does, it is for too brief a period to be of use (7). However, the observed values in the control studies were not significantly different from those reported in dogs employing the constant infusion inulin or sucrose technique in normal or nephrectomized animals (4). All animals were treated in an identical fashion and the changes in the sucrose space cannot be attributed to the method alone.

Albumin distribution using albumin ^{131}I was studied before and during the administration of dextran in nine other rabbits and in six other rabbits receiving dextran and cortisone. The methods employed to separate, purify and iodinate the protein have been described before (1). Two drops of Lugol's solution were added to the rabbits drinking water to inhibit thyroidal uptake of ^{131}I released from degraded protein. All lots of albumin ^{131}I were tested in control rabbits to insure against the use of a preparation which contained an untoward amount of denatured material. Following an intravenous injection of 50-150μC of albumin ^{131}I, heparinized bloods were obtained nine through eleven days from the opposite ear. All stools and urines were collected and assayed nine through eleven days. Albumin distribution was calculated from the distribution curve following equilibration of albumin ^{131}I between the intra and extravascular pools (6). The distribution curve is determined by correcting the plasma disappearance curve for ^{131}I lost in the blood, urine and the stool (6). The total exchangeable albumin, (TEA), was calculated as the product of the equilibrium space of albumin ^{131}I distribution (in plasma equivalents) and the serum albumin concentration. Albumin partition was defined as the ratio; total plasma albumin/TEA.

Total plasma protein was determined by a microKjeldahl method, protein

TABLE I

EXTRACELLULAR, PLASMA AND INTERSTITIAL VOLUMES

# of Studies	*Control* (*16*)	*Dextran* (*15*)	*Dextran Cortisone* (*5*)
Extracellular Volume (% Body Weight)	19.3 ± 0.8	18.8 ± 0.9	26.9 ± 0.7
% Change		−3	+43
Plasma Volume (% Body Weight)	3.4 ± 0.1	4.1 ± 0.2	6.2 ± 0.3
% Change		+21	+51
Interstitial Volume (% Body Weight)	15.9 ± 0.8	14.7 ± 0.9	20.7 ± 0.8
% Change		−8	+41
Hematocrit Value (%)	36.6 ± 0.8	27.4 ± 1.1	24.3 ± 1.7
% Change		−25	−11

Dextran group is compared to the Control group and Dextran + Cortisone to Dextran.

partition as previously described with a Kern microelectrophoresis unit (1), and dextran by the method of Roe (8).

RESULTS

Data on the body plasma volume, (PV), extracellular volume, (ECV), and the interstitial volume, (IV), calculated from the difference between the simultaneously measured ECV and PV are shown in Table I. The volume of extracellular fluid did not increase with dextran but increased 43 per cent upon the addititon of cortisone. The plasma volume increased 21 per cent in the dextran treated group associated with a 25 per cent fall in the hematocrit value. In the rabbits receiving both agents, the mean plasma volume increased an additional 51 per cent with a further fall in the hematocrit value. The calculated interstitial volume averaged 15.9±0.8 per cent in control rabbits, 14.7±0.9 per cent for those receiving dextran, and 20.7±0.8 per cent in rabbits receiving both dextran and cortisone. During dextran infusions serum albumin concentration decreased 33 per cent, (Table II). The TEA fell from 13.9±0.8 to 11.5±0.5 ($P<0.02$) with 65 per cent of this loss caused by a decrease in the circulating albumin. With dextran and cortisone, the serum albumin concentration fell only 18 per cent, (Table II), the TEA was unchanged and there was a shift of extravascular albumin back into the plasma.

Dextran levels averaged 1.7±0.3 g/100 ml of plasma in the dextran treated rabbits and 1.6±0.1 g/100 ml in the rabbits receiving both drugs. This value was

TABLE II

ALBUMIN DISTRIBUTION

	Serum Albumin g/100 ml		*Intravascular Albumin g*		*Extravascular Albumin g*	
	Dextran					
	C	*E*	*C*	*E*	*C*	*E*
# of Studies (9)						
Mean ± SE	3.6 ± 0.1	2.4 ± 0.1	5.4 ± 0.3	4.1 ± 0.2	8.5 ± 0.4	7.4 ± 0.3
% Change		−33		−24		−13
P Value		<0.001		<0.01		N.S.
	Dextran + Cortisone					
# of Studies (6)						
Mean ± SE	3.4 ± 0.1	2.8 ± 0.1	4.2 ± 0.1	5.0 ± 0.3	6.8 ± 0.2	6.0 ± 0.5
% Change		−18		+19		−12
P Value		<0.01		<0.05		N.S.

SE = Standard error of the mean
C = Control
E = Experimental
N.S. = Not significant

essentially equal to that observed in these rabbits prior to the start of cortisone, even though the plasma volume had nearly doubled.

DISCUSSION

Whereas it was initially appreciated that an increase in the plasma volume clearly follows dextran infusions (2), little was known concerning the effects of dextran infusions on extracellular volume. The present data show that the extravascular space and interstitial space do not increase with dextran. Previous studies had demonstrated that there was an expansion of the apparent space for albumin distribution, as well as a shift in distribution of albumin from intravascular areas to the extravascular space (1). In the present study extravascular albumin was again observed to be conserved. Thus, the sum of albumin and any dextran in the extravascular space would result in a higher colloid content than prior to the dextran infusions.

In the presence of both cortisone and dextran the interstitial volume increase was associated with a decrease in the amount of albumin located extravascularly. Thus, the dextran effect was reversed. Since the concentration of extravascular albumin undoubtedly differs throughout the body (9), a value for the mean interstitial albumin level would not be significant. However, there is a definite tendency for the interstitial albumin content to be maintained or raised during dextran treatment and to fall after cortisone is added.

The lack of expansion of the interstitial space during dextran administration would seem to indicate that dextran may have a limited distribution in this area. It is possible that dextran and other macromolecules may be excluded from the major fraction of this volume which is available to smaller molecules such as sucrose. This concept of excluded volumes (10,11) may also explain the difference observed in the intravascular distribution of various sized molecules, for it has been reported that dextran, fibrinogen and globulins have a smaller intravascular volume of distribution than albumin (12-15). This difference in apparent volume of distribution may be related to a smaller available volume for their distribution rather than to an albumin leak. However, without information on this point further speculation is unrewarding.

The results of this study show that dextran does not expand the interstitial volume and that the interstitial colloid content is not reduced as much as is the plasma albumin. The addition of cortisone is followed by an expanded extracellular volume and a lowered extravascular albumin content. Albumin production has been shown to be insensitive to low albumin levels per se, to decrease during dextran treatment and to increase again upon the addition of cortisone (1). The relationship between the changes in albumin distribution, interstitial volume, and albumin production warrant further investigation.

SUMMARY

1. The plasma volume and extracellular volume were determined in 15 control rabbits, 16 rabbits treated with dextran, and in five rabbits treated with dextran and cortisone. Albumin distribution was studied in 15 other rabbits treated identically.

2. Dextran infusions expanded the plasma volume but did not influence the interstitial space. Extravascular albumin was not lowered in the presence of a marked decrease in circulating albumin. The addition of cortisone resulted in an expanded extracellular and interstitial volume with a loss of extravascular albumin.

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