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PLASMA VOLUME EXPANSION BY RAPID INFUSION OF A LOW MOLECULAR WEIGHT DEXTRAN

BY

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Large infusions of a 10% solution of dextran of molecular weight 40,000 were given to dogs during 3 min using a specially designed apparatus. The initial expansion of plasma volume was about twice the volume of solution injected. Plasma volume then fell rapidly (with a half life of about 2 hr), more rapidly than the fall in dextran concentration (half-life of about 4.5 hr). Fluctuations in plasma volume and protein concentration were repeatedly observed during the return towards normal values. At 5 to 6 hr renal excretion accounted for 40% of the infused dextran, about 20% was intravascular and the remaining 40% was presumably extravascular. No dextran was found in the cerebrospinal fluid.

Dextran has been in use as a plasma volume expander for some years and the merits of various molecular weight distributions and their physiological effects have been studied. More recently attention has turned to the dextrans of lower molecular weights following the work of Gelin (1961) and his colleagues, who have shown that an improvement in blood flow follows infusion of dextran with mean molecular weight 40,000. When blood is circulated through apparatus for oxygenation or cooling (DeWall & Lillehei, 1962), problems of blood flow *in vivo* are encountered and low molecular weight dextran has been used to improve the flow (Long, Sanchez, Varco & Lillehei, 1961; Hellström & Björk, 1963). The usual method is to use dextran in the priming fluid in volumes up to 20 ml./kg body weight. Blood, saline or albumin solution may be used to complete the priming volume of the circuit. When perfusion is commenced the dextran is run into the patient very rapidly, the apparatus fills up with blood and mixing and recirculation take place until the end of perfusion. This investigation in dogs was made to define the changes which occur in plasma volume and in dextran and protein concentrations after such rapid infusions. Any loss of circulatory volume which might be due to loss of dextran from the circulation would be equivalent to haemorrhage into the apparatus and might require further infusion.

METHODS

The low molecular weight dextran used was Rheomacrodex (A.B. Pharmacia, Uppsala, Sweden) as 10% dextran in 5% glucose solution; the mean molecular weight was 40,000, 90% within the range 10,000 to 80,000. Molecular weights given in this paper will refer to mean values determined by the light scattering method. Human albumin labelled with ^{125}I (Davies, Ricketts & Bull, 1962) was used for plasma volume measurement in two dogs.

The blood cooling apparatus (Williams, unpublished) provided initial infusion at a predetermined rate with simultaneous withdrawal of the same volume of blood, the mixture being then continuously recirculated. Dogs A and D were studied using the full system for recirculation. The other four dogs received injections rapidly at a controlled rate during approximately 3 min but without extracorporeal circulation of blood.

Blood samples were taken from a femoral vein or, during perfusion experiments, from an artery. Urine samples were taken by catheter.

Dextran in serum. Protein was precipitated from 1 ml. of serum with 2 ml. of trichloracetic acid (10% w/v) and separated by centrifugation. An aliquot (1 ml.) of the supernatant solution was mixed with 4 ml. of ethanol and the faintly turbid mixture was centrifuged. Clear supernatant solution was carefully removed and the syrupy precipitate dissolved and diluted to between 50 and 250 ml. according to the dextran concentration expected. Dextran was determined on an aliquot (3 ml.) containing 50 to 100 μg of dextran, using anthrone (Roe, 1954), by comparison with standard solutions. Dilute solutions of dextran were freshly prepared each day, since dextran appeared to be lost from such solutions by adsorption on glass. The precipitation of dextran with ethanol to eliminate glucose was satisfactory at the higher dextran concentrations; at lower concentrations care was necessary in separating the small amount of syrupy dextran precipitate.

Protein in serum. The micro-Kjeldahl method was used, subtracting 0.025% of nitrogen as a small arbitrary correction for non-protein nitrogen, and multiplying by 6.25 to convert nitrogen content to protein.

Dextran in urine. Urine (5 ml.) was mixed with ethanol (20 ml.), centrifuged and the supernatant solution rejected. The precipitated dextran was dissolved in water and made up to 15 ml. Optical rotation (θ) was measured in a 10 cm tube and converted to concentration (c) using the formula $c = 100\theta/197$, where $+197°$ is the specific optical rotation for dextran.

Plasma volume. The plasma volumes were measured by the isotope dilution method using ^{125}I-albumin (Davies *et al.*, 1962), blood samples being taken 10 min after the injection and a confirmatory sample 20 min after the injection. Dextran was infused about 30 min after the albumin injection and blood samples were taken 10, 20 and 30 min later and then at 30 min intervals for the next 4.5 hr. A second plasma volume estimation was made at the end of the 5 hr experiment with a further injection of ^{125}I-albumin. The radioactivity of each of the plasma samples was measured. Radioactivity was assumed to be lost from the circulation due to mixing in the whole body albumin pool at the rate of 4%/hr as described by Baker & Wycoff (1961). No correction was made for radioactivity lost by venous sampling since the cumulative loss was not more than 3% of the total radioactivity injected. Plasma volumes were calculated by division of the total radioactivity given to the dog by the corrected radioactivity per ml. of plasma.

RESULTS

Table 1 shows the weights of the dogs, the volumes of dextran solution infused and the serum protein concentrations which might be expected at the end of infusion

TABLE 1

SERUM PROTEIN CONCENTRATIONS BEFORE AND IMMEDIATELY AFTER DEXTRAN INFUSIONS

Haematocrit values, corrected for trapped plasma, are shown in brackets

Dog	Weight (kg)	Serum protein before infusion (g/100 ml.)	Infusion (ml./kg)	Serum protein after infusion (g/100 ml.)	Expected serum protein (g/100 ml.)
A	27·0	6·06	18·5	3·47	4·10
B	15·5	6·71	9·7	5·15	5·37
C	35·0	7·69	10·0	5·54	6·09
D	13·25	6·12	37·7	2·64	3·11
E	30·5	5·62 (33)	8·2	3·95 (23)	4·63
F	12·0	6·06 (40)	20·8	3·46 (28)	3·93

assuming a plasma content of 38.5 ml./kg body weight, that is 70 ml. of blood per kg and a haematocrit of 45%. Fig. 1 shows the changes in serum protein concentration which occurred.

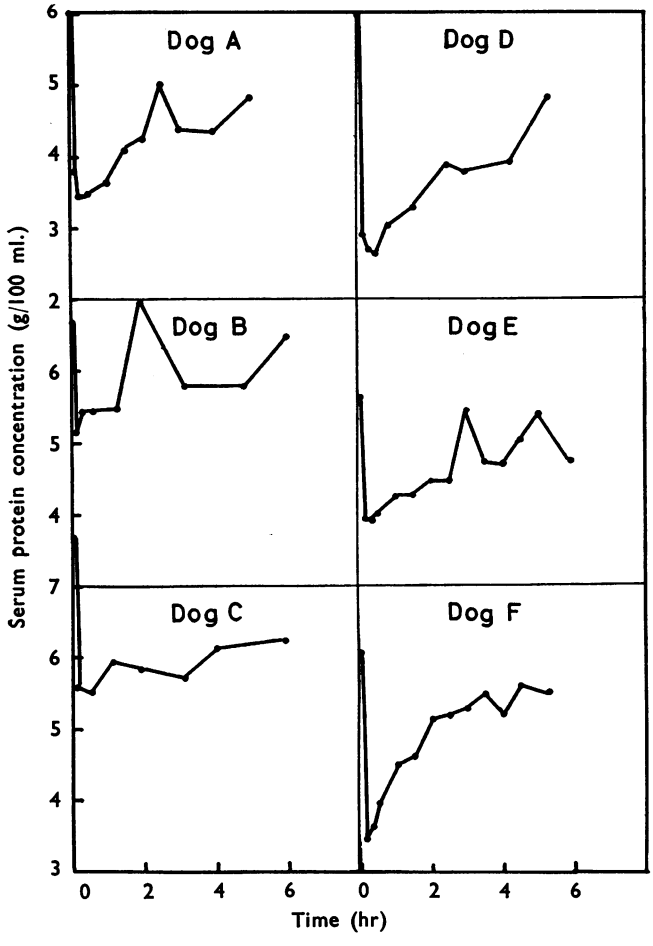

Fig. 1. Changes in serum protein concentrations of six dogs following rapid infusion of dextran of molecular weight 40,000.

The lowest serum protein concentration attained by each dog after infusion was always lower than would be expected, suggesting that the expansion of plasma volume was greater than the volume infused. Measurements of plasma volume were therefore made in dogs E and F with the results shown in Table 2. The initial expansion of plasma volume, 617 ml. in dog E and 426 ml. in dog F, was much more than the volume (250 ml.) of solution injected. The plasma volume then fell rapidly, more rapidly than the fall of dextran level, as may be seen from Fig. 2. The fall in dextran concentration approximated in the later stages to an exponential decline with a half-life of 4.5 hr. The decrease in plasma volume

TABLE 2

SERUM PROTEIN AND DEXTRAN AND PLASMA VOLUME MEASUREMENTS IN DOGS BEFORE AND AT VARIOUS TIMES AFTER DEXTRAN INFUSION

	Dog E					Dog F				
Time	Serum protein (g/ 100 ml.)	Serum dextran (g/ 100 ml.)	Plasma volume (ml.)	Total protein (g)	Total dextran (g)	Serum protein (g/ 100 ml.)	Serum dextran (g/ 100 ml.)	Plasma volume (ml.)	Total protein (g)	Total dextran (g)
Before	5·62	—	1,185	66·59	—	6·06	—	617	37·39	—
10 min	3·95	1·21	1,802	71·17	21·80	3·46	1·74	1,043	36·08	18·09
20 min	3·95	1·12	1,743	68·84	19·52	3·64	2·08	1,097	39·93	22·81
30 min	4·01	0·99	1,743	69·84	17·25	3·95	1·74	1,056	41·71	18·37
1 hr	4·26	0·70	1,547	65·90	10·82	4·49	1·03	974	43·73	9·98
1·5 hr	4·27	0·61	1,543	65·88	9·41	4·61	1·04	906	41·76	9·40
2 hr	4·47	0·53	1,493	66·73	7·91	5·14	0·84	839	43·12	7·00
2·5 hr	4·47	0·53	1,484	66·29	7·86	5·19	0·84	772	40·06	6·48
3 hr	5·36	0·53	1,446	77·5	7·66	5·27	0·71	760	40·05	5·39
3·5 hr	4·74	0·38	1,405	66·59	5·34	5·46	—	745	40·67	—
4 hr	4·69	0·38	1,480	69·41	5·62	5·19	—	784	40·68	—
4·5 hr	5·06	0·42	1,332	67·39	5·46	5·58	0·61	801	44·69	4·88
5 hr	5·39	0·38	1,295	69·80	4·89	5·49	0·58	794	43·59	4·61
5·87 hr	4·71	0·32	1,236	58·20	3·98					

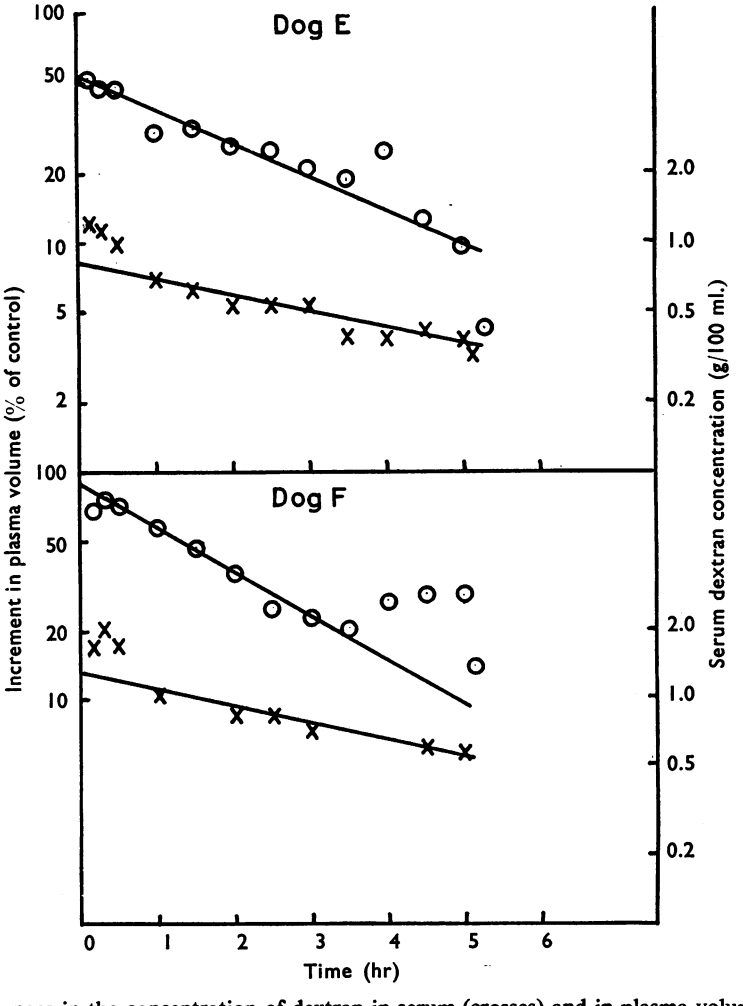

Fig. 2. Changes in the concentration of dextran in serum (crosses) and in plasma volume (circles) plotted on a log scale against time (in hr) for dogs E and F.

approximated to an exponential decline with a half-life of 2 hr. During these changes total intravascular protein showed small fluctuations, as may be seen from Table 2.

Fig. 3 shows cumulative urinary excretion curves for two dogs; dog F which had the larger dose of dextran had a poor flow of urine, while dog E had a diuresis.

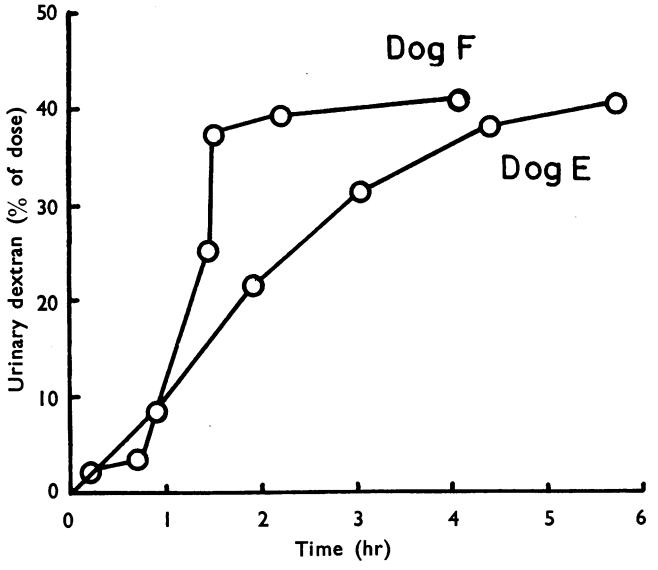

Fig. 3. Cumulative urinary excretion of dextran expressed as percentage of dose plotted against time (in hr) for dogs E and F. Dog E received 8.2 ml./kg of dextran solution, dog F received 20.8 ml./kg.

About 40% of the injected dextran was excreted during the 5 hr but the ultimate excretion would probably have been about 70% (Gelin, 1961). Less than 1% of the injected radioactivity was excreted in this time.

Five samples of cerebrospinal fluid were analysed from each of dogs E and F for total carbohydrate content; the highest values obtained were 0.037 and less than 0.01 g/100 ml. respectively.

DISCUSSION

Rapid infusion of a 10% solution of dextran with molecular weight 40,000, which has a much higher colloid osmotic pressure than plasma, leads to water entering the circulation from surrounding tissues, so increasing the plasma volume. The total increase is proportionately greater when, as in dogs B, C, E and F, dextran is simply injected and not recirculated. In dogs A and D the dextran was infused while blood was withdrawn and the whole recirculated. The intravascular volume was therefore increased in the injection group more than in dogs A and D. Plasma volume continues to increase for a short time after the cessation of a large and rapid infusion and the increase may amount altogether to as much as twice the volume injected (Table 2). The subsequent decrease in volume is comparatively

rapid and the increment of plasma volume becomes equal to the volume infused 2 or 3 hr after the infusion under these particular conditions. The fluctuations in volume found during its return to normal after the infusion seem to be genuine since they are also reflected in the protein levels which all show an unexpected decline after they have started to rise toward normal (Fig. 1). Recirculation of protein, dextran and fluid through the extracellular spaces and lymphatic system may account for this fluctuation of the blood volume, though no satisfactory conclusion about this can be drawn and alterations in splenic volume may also be implicated. The findings do suggest that there may be unpredictable changes in blood volume and that monitoring of blood volume is advisable in a perfusion circuit of this sort.

Gelin (1961) found increases in plasma volume slightly greater than the volume of dextran infused during infusions lasting 1 hr. It seems probable that slower infusions of this low molecular weight dextran would lead to smaller increases of plasma volume.

After the peak value, plasma volume falls more quickly than the concentration of dextran, despite rapid escape of dextran into tissues and through the kidney. By 5 or 6 hr the plasma volume has returned almost to normal and about 20% of the dextran is still in the circulation. It remains to be shown whether or not this dextran continues to exert a beneficial effect on blood flow. By this time renal excretion has accounted for about 40% of the injected dextran and the remaining 40% is presumably extravascular.

The very low concentration of dextran in the cerebrospinal fluid agrees with the findings of Prockop, Schanker & Brodie (1962), who showed that mannitol, sucrose, inulin and dextran enter the cerebrospinal fluid from the bloodstream extremely slowly but pass readily from the cerebrospinal fluid to blood, presumably through bulk flow of cerebrospinal fluid across a porous boundary.

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