Intravascular Persistence and Renal Clearance of Dextran of Different Molecular Sizes in Normal Children*

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During the past two decades dextran has been used extensively as a plasma volume expander in adults, while blood loss in the surgery of children is usually replaced by whole blood transfusion. Today the two main indications for using plasma expanders in children are in burns and other emergency situations when blood is not available. There is, however, increasing awareness of the complications of whole blood transfusions (Young, 1964), and there is a possibility that in future plasma expanders will be more frequently used to restore blood volume after moderate blood losses.

In recent years attention has also been drawn to the rheological properties of low molecular weight dextran (Rheomacrodex) which dissolves cell aggregates of sludged blood and promotes capillary flow in certain states of shock (Gelin and Ingelman, 1961). This may be important in neonatal surgery, where the red cell mass is often considerably increased with haematocrit values of 80% or more.

We have studied the elimination of intravenously administered dextran in 4 infants and children, seeking criteria for a suitable molecular composition of plasma expanders for use in this age-group.

Material and Methods

We studied 4 normal children, 3 boys and 1 girl, aged 6 days, 3 months, 5 years, and 8 years, who were given an intravenous injection of Rheomacrodex (average molecular weight, $\bar{M}_w$ of about 40,000, > 90% between 15,000 and 80,000) 10% in 0.9% saline.

A small test dose of 3 ml./kg. was given to minimize influencing the plasma volume. Venous blood samples were drawn at various times after the injection, and urine was collected in 5 clearance periods from each subject.

The total dextran concentration in serum and urine

was determined by the anthrone method (Wallenius, 1954). The molecular weight distribution of dextran in each sample was estimated by a gel filtration method, adapted for micro-amounts (Granath, 1966). By this method dextran is separated according to molecular size in a 'sephadex' column. The method was calibrated by a series of well-defined fractions of dextran.

The endogenous creatinine in blood and urine was determined in a Technicon auto-analyser (method N IIa). The clearance was calculated in the ordinary way, and the values reported were corrected to 1.73 m.² body surface area.

Results

The results are shown in Fig. 1-7 and Tables I and II. Fig. 1 illustrates the decrease of the total

FIG. 1.—The fall in serum dextran concentration after intravenous injection of 'rheomacrodex' (3 ml./kg.) in a normal infant aged 6 days. The same case is shown in Fig. 2-6.

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FIG. 2.—Distribution of dextran of different molecular weights in serum at different times after injection. The five curves 0-4 give results for 0, 6, 20, 40, and 60 minutes after injection. $C = \text{mg./100 ml. serum}$.

dextran concentration in serum at different times after injection, and in Fig. 2 the changes of the molecular weight distribution of dextran in serum with time after injection are shown. Dextran molecules of molecular weight of about 10,000-20,000 leave the circulation fairly rapidly, while the elimination of molecules of molecular weights $> 50,000$ is considerably slower (cf. Table I). This results in a shift towards higher molecular weights in serum as illustrated in Fig. 2. From

these data the average intravascular half-life of the different molecular sizes can be calculated as shown in Fig. 3 (cf. also Table I). The disappearance rates of the various molecular weight classes of dextran from the circulation seem to increase with increasing age of these children.

The excretion of dextran into the urine is shown in Fig. 4-7 and Table II. It is seen that approximately one-third of the injected dose is excreted in 2-3 hours. Corresponding to the shift of the molecular weight distribution of dextran in serum, towards higher molecular weight with time a similar shift was found in urine. In Table II dextran and endogenous creatinine clearance data are shown. Fig. 6 and 7 illustrate dextran clearance as a function of its molecular weight, expressed as a percentage of endogenous creatinine clearance. These preliminary data seem to show a gradual increase of the permeability to macromolecules of the glomerular membranes with increasing age.

Discussion

As has earlier been shown in animal experiments (cf. Wallenius, 1954; Grotte, 1956; Arturson, 1961) and in studies on adults (cf. Arturson and Wallenius, 1964a, b), the rate of transport of various sizes of dextran molecules across normal capillary membranes is highly dependent on the molecular weight. After intravenous injection small dextran molecules ($< 30,000$ -50,000 molecular weight) will leave the circulation faster than larger molecules ($> 30,000$ -50,000) by both the main routes—transport into the extravascular phase and excretion into the urine.

FIG. 3.—The disappearance of dextran of different molecular weights from serum after intravenous administration.

FIG. 4.—Cumulative excretion of dextran into urine after intravenous injection.

FIG. 5.—Distribution of dextran of different molecular weights in urine. 1. 10-30 min. after injection. 2. 30-50 min. after injection. 3. 50-70 min. after injection. $C = \text{mg./min.}$

FIG. 6.—Clearance of dextran of different molecular weights as percentage of endogenous creatinine clearance.

The fairly rapid shifts of molecular weight distributions in serum and urine with time was illustrated in these children, as earlier in adults. In 2-3 hours the main part of the dextran molecules still circulating will be of about 30,000-50,000 molecular weight or more. Smaller molecules have by this time already been excreted into the urine or are still in the extravascular phase on their way back to the circulating blood via the lymphatics (cf. Grotte, Arturson, Areskog, and Jakobsson, 1965). The rates of disappearance of these macro-molecules from the circulating blood seem to increase with increasing age. To some extent this may be explained by the differences in renal clearances in these 4 children. As has been shown by many workers, the inulin and creatinine clearances in the newborn period are about one-third to one-sixth of the values in adults, corrected for body surface area or total body water (cf. Vesterdal, 1959).

These studies (cf. Fig. 7) suggest that there is an

FIG. 7.—Clearance of dextran as percentage of endogenous creatinine clearance in four normal children: Case 1, aged 6 days; Case 2, aged 3 months; Case 3, aged 5 years; and Case 4 aged 8 years.

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TABLE I

Approximate Intravascular Half-life in Minutes of Different Dextran Molecular Weight Classes

Molecular Weight Classes	Case 1 (Age 6 days)	Case 2 (Age 3 mth.)	Case 3 (Age 5 yr.)	Case 4 (Age 8 yr.)
10,000-20,000	37	35	31	28
20,000-30,000	67	72	62	42
30,000-40,000	245	207	144	70
40,000-50,000	326	385	320	204
50,000-60,000	640	650	470	282

TABLE II

Clearances of Dextran and Creatinine in 4 Subjects

Case No., Sex, Weight, Length, Age, Corr. Factor	Time After Injection for Blood Sample (min.)	Plasma Dextran Concentration (mg./100 ml.)	Length of Urine Collection Period (min.)	Diuresis (ml./min.)	Urinary Dextran Excretion (mg./min.)	Dextran Clearance (ml./min.)	Creatinine Clearance (ml./min.)
1 M 2,650 g. 49 cm. 6 dy. 0.18	6 20 40 60	733 610 459 452	10 20 20 20	0.9 0.7 0.9 0.7	1.9 7.5 4.4 2.3	0.05 0.20 0.18 0.09	37
2 F 5,670 g. 51 cm. 3 mth. 0.2	10 30 50	292 215 205	12 20 20	0.3 0.8 1.3	5.1 6.3 3.5	1.4 0.9 0.5	60
3 M 16 kg. 112 cm. 5 yr. 0.72	37 57 77	279 233 201	20 20 20	4.9 5.1 4.6	16.7 13.3 7.4	5.1 4.8 3.2	21
4 M 30 kg. 135 cm. 8 yr. 1.05	41 61	183 142	20 20	4.2 7.0	42 14	30.0 11.9	59

increase in permeability of the glomerular membranes with increasing age of infants and children.

Summary

The intravascular persistence and renal clearance of dextran of different molecular sizes have been studied in 4 children aged from 6 days to 8 years. These results suggest an increase in permeability of the glomerular membranes with increasing age of infants and children.

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