Low Molecular Weight Dextran and Cardiopulmonary Bypass in the BOS Experimental Subject

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Dextrans were introduced into clinical use as plasma volume expanders in the late 1940's.[10] Since their introduction, numerous animal and clinical studies have demonstrated that the physio-chemical properties of dextrans impart various pharmacological effects on the hemodynamics of total body perfusion.

Dextran is a branched polysaccharide composed of about 200,000 glucose units. The glucose units in the main chain are bound together by 1:6 glucosidic linkages. A special strain of lactobacilli (lenconostoc Mesenteroides) converts sucrose to a highly linear dextran molecule which has a molecular weight of approximately 40 million. By means of partial acid hydrolysis and subsequent differential fractionation, this native dextran can be converted to polysaccharides of any desired range of molecular weights. The dextrans produced for clinical use are always polymolecular and are therefore defined by average molecular weight.

During World War II there was a great need for an "artificial plasma" or more specifically a plasma volume expander; thus the development of high molecular weight dextran (Dextran 70, Macrodex). Dextran 70 has an average molecular weight of 70,000. In 1950, Thorsen and Hint[14] demonstrated that dextran with a mean molecular weight greater than 60,000 caused a sharp increase in erythrocyte aggregation. They stated that "theoretically it should be possible to eliminate intravascular aggregation by the infusion of suitable low molecular weight colloids;" soon followed the development of low molecular weight dextran (Dextran 40, Rheomacrodex). Dextran 40 has an average molecular weight of 40,000 with 90% of the molecules being within the range of 10,000 to 80,000. Commercially, Dextran 40 is available as a 10% solution in .9% saline or as a 10% solution in 5% Dextrose and water.

Dextran 40, when indicated for use in pump oxygenators, has many advantages and few proven disadvantages. Dextran 40 enhances flow and capillary perfusion. This is accomplished by rapid blood volume expansion, anti-sludging, and reduction of blood viscosity. Blood volume expansion occurs due to the strong hypertonicity of the solution. It increases the oncotic pressure of plasma thereby mobilizing interstitial fluid and reducing intravascular fluid loss. A Dextran concentration of 4 Gm % exerts a colloid osmotic pressure equivalent to that of normal plasma. Expressed another way, 1 Gm of Dextran will "bind" approximately 25 ml of water. Generally, plasma volume is incrased by 1 to 2 times the volume of Dextran 40 infused. The extent and duration of volume expansion produced is dependent upon the patient's degree of hydration and pre-existing blood volume, the rapidity of infusion, and the rate of Dextran clearance by the kidney. In normally hydrated patients with adequate renal perfusion, the urine specific gravity seldom exceeds 1.040. Poorly hydrated patients

will exhibit high urine specific gravities following Dextran 40 infusion. The rate of infusion is an important factor. During the first 90 minutes following infusion, the plasma concentration falls rapidly which is mainly due to renal excretion of the smaller molecular fraction. Clearance of molecules with molecular weights of greater than 50,000 is essentially zero. Wallineous[15] demonstrated that following an infusion of 500 ml of Rheomacrodex approximately 60% is excreted within 6 hours. The higher molecular weight dextran molecules not excreted pass into the extravascular compartment. A small amount of the molecules subsequently are returned to the vascular system via the lymphatics. The remainder are removed by the reticuloendothelial system where they are degraded by dextranase to glucose.

Sludging and erythrocyte aggregation directly affect flow through capillary beds. In 1956, Gelin[5] suggested that blood sludging is a biophysical response to various types of trauma. In describing the "anemia of injury" he demonstrated that trauma caused a reduction in circulating erythrocytes greater than could be explained by actual blood loss. Further investigation showed that this decrease in circulating erythrocytes resulted from a sequestration of red cells which removed them from the effective circulating red cell mass. Gelin[5] later demonstrated that this sequestration was due to erythrocyte aggregation in the microvasculature and did not occur when low molecular weight dextran was used. Long, et. al.,[8 7] studied the microcirculation of the occular conjuctivia in both dogs and humans under normothermic and hypothermic perfusion. When Dextran 40 was not used, Long observed the formation of erythrocyte aggregates and concurrent obstruction of the microcirculation. When Dextran 40 was used this phenomenon was not observed. To achieve complete prophylaxis against aggregation, he determined that the minimum effective level of Dextran 40 was 1,400 to 1,600 mg percent. 1.0 to 1.5 Gm/kilo Dextran 40 was necessary to prevent aggregation as opposed to 2.5-3.0 Gm/kilo of albumin. In 1962, Bernstein[1] used a glass micro-electrophoresis chamber to demonstrate that low molecular weight dextran increased the repulsive forces of red cells by increasing the "zeta potential" (electronegativity).

Low molecular weight dextran increases flow and perfusion not only by increasing blood volume and preventing sludging, but also by reducing viscosity. An increase in cohesive forces causes an increase in peripheral resistance thereby reducing flow. High viscosity in the microcirculation favors hypoxia by delaying passage of red cells and also by decreasing the diffusibility of oxygen. Both Rand and Suzuki[11 13] demonstrated that blood and plasma viscosity is not appreciably effected by the addition of heparin. Normal saline will reduce viscosity through dilution but the effects are only transient due to rapid loss from vascular system.[12]

The flow improving properties of Dextran 40 should make total body perfusion more effective. Dextran 40 not only helps maintain adequate perfusion of vital organs, but also increases urine output and reduces hemolysis. Arteriography[4] has shown that Dextran 40 helps to maintain normal distribution of blood flow in the kidney. Dextran molecules with a molecular weight of less than 15,000 have the same renal clearance as creatinine and are able to pass the glomecular membrane without restriction. The active diuresus of the lower molecular weight component exerts significant protective influence against the accumulation of nephrotoxic agents.

Rheomacrodex is the most effective nonhemic solution in the prevention of hemolysis and thrombocytopenia. In a comparison of 5% albumin, rheomacrodex,

and whole blood as priming fluids for human cardiopulmonary bypass, both Long[8] and Mainardi[9] found a direct relationship to hemolysis in the Dextran 40 group. With Dextran 40 there was a 42% decrease in plasma free hemoglobin per minute of bypass as opposed to only a 19% decrease with albumin. Brewer[3] has reported a sthenoplastic effect of dextrans on platelets. Platelets in the presence of Dextran 40 are more resistant to the disruptive effect of ultrasonic energy. This effect possibly explains why "Dextran coated" platelets do not readily lyse as a result of trauma.

In addition to the desirable attributes of increased flow and tissue perfusion, increased urine output, and reduced hemolysis, dextrans possess a few less desirable characteristics. Dextran is a potent antigen. In man the subcutaneous injection of only 1 mg maximum leads to the development of precipitins and cutaneous wheal reactions. Therefore, the antigenic activity of dextran would seem to preclude its repeated use. However, when administered in the massive doses that are employed for infusion, antibody production does not occur. This is due presumably to the phenomenon of "immunological paralysis" and to the fact that Dextran has a very low degree of side chain branching.

In addition to rare antigenic effects, dextrans have been implicated in bleeding problems. However, a review of the literature reveals that serious hemostatic defects have been reported only when doses greater than 20 mg/kg have been administered. Long,[8] Breckenridge,[2] and Glass[6] have demonstrated that reported bleeding problems were due to the large molecular weight fraction. When high molecular weight dextran was used in extracorporeal circulation, platelet counts and fibrinogen levels decreased and prothrombin times increased. When low molecular weight dextran was used these parameters were not appreciably effected and bleeding problems were not encountered.

In a recent study at the Texas Heart Institute, it was demonstrated that Dextran 40 is useful in the maintenance of satisfactory perfusion flow rates and in the reduction of tissue and pulmonary edema.

Total cardiopulmonary bypass of 120 minute durations permitted implantation of Total Artificial Heart Prostheses in 26 successive bovine calves. Calf weights ranged from 64 to 102 kg. Succinyl choline and halothane anesthetic were used to achieve desired anesthesia levels. Total heparinization was achieved using beef lung heparin (3 mg/kg) prior to cannulation. Arterial cannulation was to the left common carotid artery cephalically and the left femoral artery caudally. The inferior vena cava was cannulated through the right atrium, and superior vena cava cannulation was through the left jugular vein. The extracorporeal circuit was primed and total normothermic cardiopulmonary perfusion was initiated.

The first prime used in this series consisted of fresh donor blood and 5% Dextrose in Ringer's Lactate solution (D_5RL). Extreme hemodilution and decreased perfusion rates necessitated the addition of large amounts of citrate phosphate dextrose (CPD) blood and D_5RL (2000-6300cc). With regard to maintenance of adequate flow rate, this treatment proved either transiently effective or totally ineffective. The first 5 perfusions demonstrated severe intraoperative fluid shifts away from the intravascular compartment. Autopsies on calves sacrificed immediately following cardiopulmonary bypass demonstrated respiratory insufficiency of pulmonary edamatous origin, severe ascites, and cerebral edema. Imparied or absent renal function and progressive metabolic acidosis resulted from grossly unusual

vascular dynamics during cardiopulmonary perfusion. Platelet-leukocyte aggregation repeatedly occluded the extracorporeal microemboli filtering system.

Primary modifications were instituted in an attempt to rectify these problems. 1000 ml of fresh donor blood plus 1000 ml of D_5RL plus 500 ml of 10% low molecular weight dextran in normal saline (Dextran 40) was used to prime the circuit.

Normothermic extracorporeal perfusion was regulated primarily by the rate of perfusion flow with secondary regard to changes in mean arterial blood pressure. Flow rates between 45 and 55 ml/kg/min were considered optimal. Flow rates less than 40 ml/kg/min prompted fluid addition to the circulatory volume. A minimum hemoglobin concentration of 5 Gm % and a minimum hematocrit of 15% were values used as a regulation point in fluid balance and hemodilution. Flow rates were not sacrificed to correct increasing mean arterial blood pressures. During bypass attempts were made to pharmacologically maintain mean arterial pressure between 40 mmHg and 80 mmHg.

Table I summarizes the prime, weight, hemoglobin, pH and flow relationships. The 2500 ml Dextran 40-D_5RL-blood prime significantly improved maintenance of constant optimum flow rates without endangering oxygen capacities due to excessive hemodilution. These optimum arterial flow rates were easily obtainable during all cases which included the Dextran 40-D_5RL-blood priming solution. As seen in Table I, lower flow rates occurred when Dextran 40 was eliminated from the priming solution.

TABLE I

Summation of Prime, Weight, Hemoglobin, pH, and Flow Relationships:

No. of Cases	Prime	Mean Wt	Mean Flow
5	Blood + D RL 1000 cc 1500 cc	82.6	37.6
21	Blood + D RL + Dextran 1000 cc 1000 cc 500 cc	83.6	54.1

No. of Cases	Mean Hbg Low/End	Mean pCO	Mean pH Arterial	Urine cc
5	6.68/6.92	40.8	7.296	30
21	6.74/7.23	42.2	7.347	240

As shown in Table II, the addition of fluid following initiation of extracorporeal perfusion was unnecessary in one-half of the cases. In Group II, the entire group averaged only 233 ml added during bypass. Group I, in which Dextran 40 was omitted from the prime, averaged 1700 ml fluid added during bypass. Initial hemodilution resulted in hemoglobin concentrations of greater than 5.4 Gm % and rarely diluted concentrations below 6.2 Gm %. End hemoglobin concentration averaged 7.23 Gm %. The average urine output without Dextran 40 was 30 cc as opposed to 240 cc with Dextran 40. No diuretics were used during cardiopulmonary bypass and administration of alkalizing agents was not necessary.

TABLE II

Total Fluid Added
During Bypass

GROUP 1 Non-LMWD	GROUP 2 LMWD
1-6300	11-0
1-1500	7-500
1-2000	2-200
1-500	1-1000
1-3000	
Ave. = 2660	Ave. = 233

It was demonstrated in 21 consecutive bovine calf perfusions that the addition of Dextran 40 to a blood D_5RL prime was accompanied by an increase in venous return, a reduction in fluid shifts, and maintenance of satisfactory perfusion flow rates. It can also be stated that Dextran 40 increases urine output, reduces platelet-leukocyte aggregation, and functions in the preservation of capillary membrane integrity thereby discouraging ascites and pulmonary edema which previously occurred during extracorporeal circulation.

REFERENCES

1. Bernstein, E. F., Emmings, F. G., Mackey, G. C., Castaveda, A. E., Varco, R. L.: Effect of Low Molecular Weight Dextran and Red Cell Charge During Extracorporeal Circulation. Trans Amer Soc Artif Intern Organs. 8:23, 1962.

2. Breckenridge, I. M., and Walker, W. F.: Blood-Loss in Open-Heart Surgery with Low-Molecular-Weight Dextran. Lancet. 1:1190, (June 1) 1963.

3. Brewer, S., Jr.: The Stethenoplastic Effect of Dextran on Platelets—The Mechanism for Prevention of Thromboembolism. Abstr 10th Cong Int Soc Haematol. Stockholm, 1964.

4. Finsterbush, W., Long, D. M., Jr., Sellers, R. D., Amplatz, K., and Lillehei, C. W.: Renal Arteriography During Extracorporeal Circulation in Dogs with a Preliminary Report Upon the Effects of Low Molecular Weight Dextran. J. Thorac Cardiov Surg. 41:252, (Feb.) 1961.

5. Gelin, L. E.: Studies in Anemia of Injury. Acta Chir Scandinav. Suppl 210, 1956.

6. Glass, B. A., Albert, H. M., and Shelby, J. S.: Hemodilution Perfusion in Rotating Disc Oxygenators. Amer Surg. 31:184, (March) 1965.

7. Long, D. M., Jr., Sanchez, L., Varco, R. L., Lillehei, C. W.: The Use of Low Molecular Weight Dextran and Serum Albumin as Plasma Expanders in Extracorporeal Circulation. Surgery. 50:12, 1961.

8. Long, D. M., Jr., Folkman, M. J., McClenathan, J. E.: The Use of Low Molecular Weight Dextran in Extracorporeal Circulation, Hypothermia, and Hypercapnea. J Cardiov Surg. 4:617, (August) 1963.

9. Mainardi, L. C., Bhanganada, K., Mack, J., and Lillehei, C. W.: Hemodilution in Extracorporeal Circulation: Comparative Study of Low Molecular Weight Dextran and 5% Dextrose. Surgery. 56:349, (August) 1964.

10. Pharmacia: Rheomacrodex—Flow Improver in Adjunctive Therapy of Shock. Pharmacia. 1968.

11. Rand, P. W., Lacombe, E., Hunt, H. E., Austin, W. H.: Viscosity of Normal Human Blood Under Normothermic and Hypothermic Conditions. J Appl Physiol. 19:117-122, 1964.

12. Schenk, W. G., Jr., Delin, N. A., Domaning, E., Hahnloser, P., and Hoyt, R. K.: Blood Viscosity as a Determinant of Regional Blood Flow. Arch Surg. 89:783, (November) 1964.

13. Suzuki, M., and Penn, I.: The Effect of Therapeutic Agents Upon the Microcirculation During General Hypothermia. Surgery. 60:867, 1966.

14. Thorsen, G. and Hint, H.: Aggregation, Sedimentation, and Intravascular Sluding of Erythrocytes. Act Chir Scandinav. Suppl. 154, 1950.

15. Wallenius, G.: Renal Clearance of Dextran as a Measure of Glomerular Permeability. Acta Soc Med Upsal Suppl 5, 1954.