Prevention of Excess Hemolysis During Cardiopulmonary Bypass by the Use of Mannitol

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Acute renal failure following extracorporeal circulation has been observed in about three of every 100 unselected cases.1, 2 The occurrence of hemoglobinuria, jaundice, and indirect bilirubinemia suggested to us that hemolysis in excess of that normally expected might be contributing significantly to this problem. All of the cases in one series1 underwent operations involving the aortic valve that required extracorporeal circulatory support exceeding two hours.

Although pump hemolysis was investigated extensively during the early phase of open-heart surgery,3 reappraisal was deemed important in light of recent improvements in operative technique4 which have led to the use of longer periods of cardiopulmonary bypass. It was during this reappraisal that a correlation between plasma hemoglobin concentration and renal shutdown was documented.1 This was considered of sufficient importance for us to undertake a systematic plan to reduce plasma hemoglobin concentration. Attempts to decrease red cell trauma by changing blood collection techniques and/or containers were unsuccessful. More recently, the production of an osmotic diuresis during the time of bypass has given promising results.

Methods

Ten ml. of heparinized blood was drawn into siliconized syringes. Samples were taken either from the patients' indwelling venous catheters or, at 15-minute intervals, from the heart-lung machine, depending on the stage of the operation. After 15 minutes of centrifugation, the plasma was aspirated and analyzed in a Beckman spectrophotometer (model DK-1 or DU) for hemoglobin content.5 The remaining plasma was used to determine mannitol content by the method of Corecoran and Page.6 Urinary hemoglobin was measured by the method of Crosby and Furth.7 Haptoglobin binding capacity was determined by electrophoresis. The method has been described elsewhere.1

Prior to positioning on the operating table, all patients who received mannitol had an indwelling catheter inserted into the bladder and subsequent volumes recorded and fractionally analyzed for mannitol, hemoglobin, and electrolyte content.

Initially, mannitol was given as a drip as described by Barry et al.8 However, due to a 30- to 45-minute delay between the start of the mannitol infusion and the onset of diuresis, presumably representing saturation of the mannitol space (ECF), this procedure was abandoned. Instead, 20 per cent mannitol solution was added to the heart-lung machine prior to bypass, to establish a plasma level of 500 mg. per cent (26.7 mOsm./L. plasma). A replacement drip, begun one-half hour after the onset of bypass, based on the assumption of 50 per cent of normal glomerular filtration rate (GFR),9 was continued throughout the bypass. Formulas for calculating the amounts of mannitol are:

I. Mannitol for pump priming:

ECF + PVpump × 5 = grams of mannitol

II. Mannitol replacement drip:

50 per cent estimated GFR × 5 = mg./min. of mannitol

ECF = 20 per cent of Kg. body weight expressed in liters

PVpump = 55 per cent of pump blood volume expressed in liters

5 = factor to give estimated plasma mannitol concentration of 500 mg. per cent

Estimated GFR = 120 ec./min./1.73 M.2

Initially, mannitol was administered after the termination of bypass to some patients whose maximum plasma hemoglobin values exceeded 100 mg. per cent. Since all patients had adequate urine flow postbypass, this has been discontinued.

Results

The hemoglobin build-up rate, expressed in mg. per cent per hour, has been used to assess
the effect of mannitol on hemolysis. Previous observations\(^1\) revealed that a near-linear rise of plasma hemoglobin occurred when plotted against time. Figure 1 depicts this plotted relationship. The Y intercept represents the extrapolation to time zero \((t_0)\) of the plasma hemoglobin content of the extracorporeal circuit after dilution with the patient's plasma. Point \(B\) is the mean value for the in vitro haptoglobin binding capacity of 100 open-heart patients, and is expressed as mg. per cent hemoglobin. The slope of the line \((M)\) gives the rate of hemoglobin accumulation in the plasma.

Analysis of the data in 68 patients who did not receive mannitol revealed a correlation between operative procedure and high plasma hemoglobin concentrations occurring during bypass (fig. 2). Since the two patients in whom renal failure occurred had plasma hemoglobin concentrations in excess of 200 mg. per cent, this correlation was used to select patients for mannitol administration. Three groups could be distinguished with regard to their hemoglobin build-up rate and maximum hemoglobin concentration: (1) aortic valvular replacement; (2) total correction of tetralogy of Fallot, especially in patients over 16 years of age; and (3) any patient whose lesion required a bypass of 120 minutes or longer (mitral valvular replacement or complicated congenital cardiac disease). Forty patients were considered preoperatively to fall into one of these groups and have received mannitol.

By comparing the hemoglobin build-up rate
in similar operative categories, with and without mannitol (fig. 3), the effects of mannitol are obvious. Patients who required replacement of the aortic valve by a Starr-Edwards prosthetic valve were selected for further comparison (fig. 4) since they constituted the largest group receiving mannitol. The plasma hemoglobin build-up rate was more significantly \((P < 0.001)\) reduced by mannitol in this group. It is important to note that this reduction occurred before renal excretion of hemoglobin was present.

In addition, with mannitol, there appeared to be no difference between the plasma hemoglobin build-up rate while hemoglobin was completely bound to haptoglobin and nonfilterable, and after it appeared free in the plasma, filterable by the glomerulus. It is of interest that mannitol appears to lower significantly the haptoglobin binding capacity. Further studies to confirm and elucidate this are in progress.

These observations suggest that some mechanism other than renal excretion explains the effect of mannitol on hemoglobin build-up rate in the plasma. The possibility of a decrease in red cell breakdown is being investigated currently.

Analysis of the urine from all mannitol-treated patients during bypass and the 24 hours immediately following revealed total hemoglobin values from 0 to 560 mg. The maximum recovered from any patient undergoing aortic operation was less than 200 mg., an insignificant amount compared with the decrease in plasma hemoglobin build-up rate produced by mannitol. Mannitol recovery in the same period averaged 62 per cent of that administered. In no patient did either sodium of potassium excretion exceed 75 mEq. in that period, and generally values were much less.

**Summary**

Mannitol infusion has significantly decreased plasma hemoglobin build-up rate in mitral and aortic valvular replacement. This occurred before hemoglobin appeared in the urine, and was unrelated to the binding of hemoglobin by haptoglobin. The mechanism by which mannitol decreases the build-up rate of plasma hemoglobin is unknown, but seems to be other than by renal excretion of hemoglobin.

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**References**

2. Doberneck, R. C., Reiser, M. P., and Lillehei, C. C.


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