The effects of mannitol on blood viscosity

ALLAN M. BURKE, M.D., DONALD O. QUEST, M.D., SHU CHIEN, M.D., PH.D., AND CESARE CERRI, M.D.

Departments of Neurological Surgery, Neurology, and Physiology, Columbia University, New York, New York

To determine the effect of mannitol on blood viscosity, serial measurements were carried out on venous blood in patients undergoing craniotomies for intracranial aneurysms. Blood samples were drawn immediately prior to, and 30 minutes, 2, and 4 hours after administration of mannitol. Complete blood counts, serum osmolarities, and erythrocyte microsieving studies were also performed on each sample. Whole-blood viscosity decreased at 30 minutes and 2 hours, but not at 4 hours after mannitol administration. This decrease appeared at high shear rates only, where erythrocyte deformability is critical in determining viscosity. This effect was independent of the hematocrit. Removal of mannitol from the suspension returned red cell deformability to preadministration values, indicating that the increased erythrocyte deformability required the presence of mannitol and the relative hyperosmolality induced by this agent. The reduced erythrocyte rigidity and subsequent decreased whole-blood viscosity should enhance tissue perfusion in the microcirculation.

KEY WORDS □ mannitol □ blood viscosity □ erythrocyte deformability □ cerebral ischemia □ blood flow

MANNITOL is one of the most useful drugs in the neurosurgeon’s armamentarium. Its beneficial effect of osmotically dehydrating the brain is well known. In addition, it is known to decrease cerebrovascular resistance and increase cerebral blood flow.5,8,13 It has been postulated that its beneficial effects in models of acute cerebral ischemia may be due to all of these factors and possibly also to a reduction in blood viscosity.1,9 This study was undertaken to elucidate the precise effects of mannitol on blood viscosity and to attempt to define the rheological mechanisms responsible for these effects.

Clinical Material and Methods

Eleven patients undergoing surgery for intracranial aneurysms were studied. Each patient received mannitol, 1 gm/kg intravenously, during the initial portion of the operation. Heparinized venous blood samples were obtained from all patients immediately before administration of mannitol, and 30 minutes, 2, and 4 hours later. Surgery proceeded uneventfully in all patients; standard crystalloid intravenous solutions were used for replacement, without the use of blood or colloid administration.

Serial viscosity measurements were performed on whole blood, plasma, red blood cell suspensions in autologous plasma at controlled hematocrit, and red blood cell suspensions in buffered Ringer’s albumin solution. These data were correlated with plasma osmolarity, plasma protein concentrations, and complete blood counts. Timed passage of red blood cells through polycarbonate microsieves was also carried out as a method to ascertain red blood cell deformability. Assessment of the data allowed not only specific measurement of viscosity changes, osmotic effects, and hemodilution caused by mannitol but also definition of the biophysical mechanisms by which the effects occurred.

The viscosity measurements were performed in an air-bearing coaxial cylinder (Couette) viscometer originally designed by Gilinson, et al.,6 and modified in our hemorheology laboratory. All studies were performed at 37°C, and at shear rates of 0.52, 5.2, 52, 104, and 208 reciprocal seconds (sec−1). At controlled
Mannitol and blood viscosity

temperature, four major factors influence blood viscosity: 1) plasma viscosity; 2) hematocrit; 3) red blood cell aggregation; and 4) red blood cell deformability. Each of these factors was evaluated in turn. Since plasma does not contain solid particles, its viscosity does not vary with different shear rates; the values obtained at 5.2 and 0.52 sec\(^{-1}\) were averaged. Viscosity measurements of whole blood were performed on each sample at the above five shear rates. The viscosity of erythrocytes suspended in autologous plasma at a controlled hematocrit of 45% eliminates hematocrit as a variable and reflects the influence of red blood cell aggregation at low and intermediate shear rates and red blood cell deformability at high shear rates. The viscosity of washed erythrocyte suspensions at 45% hematocrit in buffered Ringer-albumin was determined in order to assess intrinsic red cell deformability independent of influences of plasma.

The resistance of 1.5% red blood cells in Ringer's albumin solution relative to the resistance of the solution alone on passage through polycarbonate sieves with 3-μm pore size was measured and utilized as an additional index of intrinsic red blood cell deformability independent of interactions with plasma.

Hematocrit, hemoglobin concentration, red blood cell counts, plasma protein concentration, plasma protein fractions, and fibrinogen were all determined in the standard fashion. Mean corpuscular volume and mean corpuscular hemoglobin concentration were calculated. Plasma osmolarity was measured by the freezing-point depression method.

The data were evaluated statistically using measurements made immediately prior to the administration of mannitol compared with those of each of the three later samples. Significance was determined using the ANOVA system for completely randomized design, which permits assessment of the influences of several parameters over time.

Results

Viscosity

The serial determinations after administration of mannitol for whole-blood viscosity are shown in Fig. 1. Values measured at 52, 104, and 208 sec\(^{-1}\) were chosen to illustrate high shear rates as the effect of mannitol was demonstrated only there, and high shear rates exist in arterioles and capillaries where oxygen delivery occurs. There was a significant reduction in blood viscosity within 30 minutes after mannitol administration, and the effect increased as shear rate increased. The effect was less but still statistically significant (p < 0.005) at 2 hours after administration. At 4 hours, no significant reduction in viscosity was demonstrable.
FIG. 3. Serial changes in viscosity of erythrocytes suspended in autologous plasma at controlled hematocrit of 45% red blood cells immediately prior to and following administration of mannitol.

plasma affords a measure of the fourth factor, red blood cell deformability in the presence of plasma constituents. However, such viscosity studies do not distinguish between intrinsic red blood cell properties and interactions of erythrocytes with plasma.

When plasma is removed, and the erythrocytes washed and then suspended at a 45% hematocrit in buffered Ringer’s albumin solution, aggregation is eliminated, thus allowing measurement of intrinsic erythrocyte deformability independent of interactions with plasma. Figure 4 demonstrates that no change in viscosity of erythrocytes suspended in Ringer’s albumin solution occurred at any shear rate during the entire 4-hour period studied. Thus, although erythrocyte deformability was increased in plasma with mannitol present, intrinsic red blood cell deformability returned to normal in an isosmolar mannitol-free medium.

Microsieveing

The forced passage of washed erythrocytes suspended in buffered Ringer’s albumin solution through 3 μm pore polycarbonate sieves caused no significant change. These data support those above in that the increased erythrocyte deformability occurred only in the presence of plasma and mannitol. Serial changes following the administration of mannitol are shown in Table 1. Serum osmolality rose, as expected, from a mean of 281 mOsm to 293 mOsm 30 minutes after mannitol administration. By 4 hours, the osmolality had decreased to 286 mOsm. Hematocrit decreased during the 4 hours, mainly because of the increased plasma volume due to the osmolar effects of mannitol. Mean corpuscular volume also decreased significantly from 89.9 to 79.0 cu μm. Plasma protein concentration, plasma protein fractions, and fibrinogen concentration showed no significant change during the study.

Discussion

The four major factors influencing blood viscosity when temperature is held constant are: 1) plasma viscosity; 2) red blood cell concentration (hematocrit); 3) red blood cell aggregation; and 4) red blood cell deformability.

Plasma viscosity was shown in this study to be unchanged by mannitol administration. Therefore, a change in plasma viscosity is not a responsible mechanism for the reduction in whole-blood viscosity demonstrated. Plasma protein concentration, plasma protein fractions, and fibrinogen concentrations were also unchanged throughout.

Variation in red blood cell concentration (hematocrit) is the major factor influencing blood viscosity. Certainly the decreased hematocrit due to increased plasma volume observed with mannitol is a major factor in the viscosity reduction noted. However, when hematocrit is controlled at a standard 45%, a reduction in viscosity was still seen in this experiment, implying that decreased red cell aggregation and/or increased red cell deformability are responsible.

Blood is a non-Newtonian fluid, that is, its viscosity is shear-dependent. Blood viscosity increases markedly as shear rate decreases toward zero, and this is caused by red blood cell aggregation due to bridging of cell surfaces by fibrinogen and other plasma proteins. At high shear rates (52, 104, and 208 sec⁻¹), the aggregating forces are overcome. As shown in this
Mannitol and blood viscosity

Blood viscosity influences prognosis in acute ischemic conditions, such as myocardial infarction, and contributes significantly to vascular resistance in critically ill patients. In this study, mannitol has been demonstrated to have the beneficial effect of lowering blood viscosity by decreasing hematocrit, by decreasing red blood cell volume, and by increasing red blood cell deformability — all of which should enhance tissue perfusion in the microcirculation.

Acknowledgments

The authors wish to thank Mr. Daniel Batista, Mr. Juan Rodriguez, and Ms. Dagmara Igals for their excellent technical assistance. We also thank Ms. Roni Taborn for the secretarial preparation of this manuscript.

References


TABLE 1

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Hematocrit (%)</th>
<th>MCV (cu #m)</th>
<th>Osmolarity (mOsm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>39.8 ± 4.21</td>
<td>89.8 ± 2.97</td>
<td>281 ± 6.1</td>
</tr>
<tr>
<td>0.5</td>
<td>35.2 ± 3.68</td>
<td>79.7 ± 2.49</td>
<td>293 ± 5.5</td>
</tr>
<tr>
<td>2</td>
<td>33.6 ± 4.71</td>
<td>80.0 ± 1.76</td>
<td>289 ± 5.4</td>
</tr>
<tr>
<td>4</td>
<td>33.1 ± 3.77</td>
<td>87.9 ± 1.91</td>
<td>286 ± 5.7</td>
</tr>
</tbody>
</table>

* MCV = mean corpuscular volume. Values are means ± standard error of the means.

This study shows that mannitol reduces red blood cell rigidity, which should allow for a freer passage of the red cells through small blood vessels. In addition, the decrease in mean corpuscular volume, due to the osmotic effect of mannitol on the red cell itself, should further enhance microperfusion. This change in the mean corpuscular volume, independent of hematocrit, correlated well with the viscosity changes measured and with the changes in serum osmolarity (Table 1).

Several studies have noted decreased red blood cell deformability when the cells were suspended in hyperosmolar media. However, this decrease in deformability occurred at osmolarities from 350 to 600 mOsm, far exceeding the increased osmolarity observed from mannitol administration in the patients in this study. Other studies of red cell behavior at osmolarities from 275 to 300 mOsm have confirmed an increase in deformability that we infer from this study.

J. Neurosurg. / Volume 55 / October, 1981