The Effects of High Dose Mannitol on Cerebral Blood Flow in Dogs with Normal Intracranial Pressure


SUMMARY In normal dogs, bolus administration of a very high dose of mannitol (2 gm/kg) resulted in a small, transient increase in cerebral blood flow (CBF) of approximately 8 percent lasting less than 10 minutes followed by a significant reduction in CBF of approximately 20 percent lasting at least three hours. The increase in CBF may in part be related to changes in cardiovascular and hematological parameters. No explanation is available for the reduction below control values but, since urine losses were not replaced in these animals, changes in the state of hydration may have been responsible. It appears that the increase in CBF resulting from mannitol administered by bolus infusion are of neither sufficient magnitude nor duration to explain the protective effect observed in other studies where cerebral blood flow was reduced below ischemic levels. This suggests then, that either the effect of mannitol on CBF is quantitatively different when flow is reduced to critical levels or that the protective effect observed when the cerebral circulation is compromised is based upon a different mechanism than augmentation of flow. Further studies on the effect of mannitol on CBF in ischemic situations, where the cerebral circulation is compromised, are required.

HYPERTONIC mannitol has been used extensively to decrease brain bulk intraoperatively and treat intracranial hypertension associated with a variety of neurological disorders. Under certain circumstances, mannitol has also been shown to increase cerebral blood flow (CBF) in normal and brain injured animals and humans. Furthermore, it appears to have a protective effect on tissue viability during temporary and permanent arterial occlusion. The purpose of this study was to document the changes in cerebral blood flow (CBF) in normal dogs which result from bolus injection of very high doses of hypotonic mannitol.

Materials and Methods

Male mongrel dogs weighing between 10 and 15 kg were used for this study. Anesthesia was induced with intravenous chloralose (75 mg/kg) and urethane 500 mg/kg, and maintained with nitrous oxide/oxygen mixture (75%:25%) supplemented with intravenous morphine (1-4 mg/kg total) as needed. Muscular paralysis was produced with intravenous pancuronium (.5 mg/kg) supplemented as needed and ventilation was controlled with a pump respirator. The animals were hyperventilated and PaCO$_2$ were hyperventilated and PaCO$_2$ were maintained at 30 mmHg. Heart rate (HR) was derived from the electrocardiogram. A permanent record of the physiological parameters was made on an 8 channel strip chart recorder.

Samples of arterial blood were drawn prior to each blood flow measurement for determination of PO$_2$, PCO$_2$, pH, serum electrolytes, glucose, and blood urea nitrogen. Hematocrit (HCT) and osmolality were measured at the beginning and end of each experiment.

In 14 animals, a single 2 gm/kg bolus of 20% mannitol was injected over seven minutes. CBF was determined before, and at 5, 10, 20, and 30 minutes subsequent to completion of the bolus in five animals and before, and at 30, 60, 120, and 180 minutes in nine animals. Urine losses were not replaced.

Cerebrovascular resistance was estimated by dividing the difference between mean systemic arterial and central venous pressures by the mean total cerebral blood flow. Subsequent values of mean total cerebral blood flow are expressed in ml/100 gm/min. All data are ex-
pressed as the mean ± SEM and were analyzed utilizing analyses of variance. Values of P ≤ 0.05 were considered significant.

**Results**

Throughout the course of the study, core temperature and arterial blood gases remained essentially constant with the exception of a gradual decline in arterial pH indicative of a mild metabolic acidosis (table 1). Following administration of mannitol, the end tidal CO₂ increased abruptly which necessitated a reduction in the inspired CO₂ concentration in order to maintain PACO₂ at 30 torr. This perturbation lasted less than 10 minutes in most instances.

Mean arterial pressure increased from a control value of 115 ± 11 torr to 125 ± 16 five minutes after completion of the mannitol bolus, to 128 ± 21 at 10 minutes and returned to control levels by 30 minutes. Central venous pressure was initially 7 ± 1 torr, increased to 10 ± 1 at 5 minutes and returned to control value at 30 minutes. Heart rate increased abruptly from 81 ± 12 beats per minute to 115 ± 19 at 5 minutes, falling to 75 ± 12 at 30 minutes, returning to the control value by 60 minutes. None of these changes were statistically significant except the increase in heart rate at 5 minutes.

Total mean cerebral blood flow increased from a control of 42 ± 3 to 46 ± 6 at five minutes and then declined below control values to reach a plateau of approximately 34 where it remained for the duration of the study. A similar pattern of changes was noted for cerebral hemisphere, cerebellar and brainstem flow when considered individually. None of the changes in flow were statistically significant except the decrease below control values at 30 minutes. Following administration of mannitol, cerebrovascular resistance increased from a control value of 2.7 units to 3.4 at 30 minutes and 3.9 at 180 minutes.

Serum BUN and potassium did not change significantly throughout the study. Administration of mannitol produced a reduction in serum sodium from control of 155 ± 2 mEq/L to 134 ± 1 at five minutes which gradually returned to control levels by 180 minutes. A similar change was noted in hematocrit. Serum osmolarity increased from a control value of 321 ± 4 mOsm/L to 351 ± 6 at five minutes and then gradually declined toward control values at 180 minutes.

**Discussion**

The role of hypertonic mannitol in decreasing brain bulk and treating intracranial hypertension is well established. Following administration of mannitol in these situations, neurological deficits often improve. The changes in clinical condition are usually attributed to CBF increasing above ischemic thresholds as a result of lowered intracranial pressure (ICP) and increased perfusion pressure. However, the underlying mechanisms are undoubtedly more complicated. Mannitol has been demonstrated to increase CBF in brain injured animals and man without altering cerebral perfusion pressure, while conversely, in other instances no increase in CBF has been noted even though ICP decreases.

A number of investigators have demonstrated a protective effect of mannitol in situations where the cerebral circulation has been compromised. These beneficial effects appear to be independent of the brain shrinking action of mannitol. Pretreatment with mannitol prevents the “no reflow” phenomenon from occu-

### Table 1 Effect of Mannitol Bolus

<table>
<thead>
<tr>
<th>Control (ml/100 gm/min)</th>
<th>Time (minutes) post mannitol</th>
<th>5</th>
<th>10</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CBF</td>
<td>42 ± 3</td>
<td>46 ± 6</td>
<td>40 ± 4</td>
<td>38 ± 2</td>
<td>34 ± 3</td>
<td>34 ± 5</td>
<td>41 ± 9</td>
</tr>
<tr>
<td>Hemispheres</td>
<td>43 ± 3</td>
<td>43 ± 5</td>
<td>38 ± 4</td>
<td>36 ± 3</td>
<td>35 ± 3</td>
<td>35 ± 5</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>43 ± 3</td>
<td>48 ± 4</td>
<td>41 ± 3</td>
<td>40 ± 2</td>
<td>35 ± 3</td>
<td>35 ± 5</td>
<td>44 ± 9</td>
</tr>
<tr>
<td>Brainstem</td>
<td>36 ± 2</td>
<td>36 ± 3</td>
<td>31 ± 3</td>
<td>28 ± 2</td>
<td>30 ± 3</td>
<td>30 ± 4</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>MAP (torr)</td>
<td>115 ± 11</td>
<td>125 ± 16</td>
<td>128 ± 21</td>
<td>123 ± 16</td>
<td>114 ± 9</td>
<td>112 ± 12</td>
<td>118 ± 14</td>
</tr>
<tr>
<td>CVR (mmHg/ml/min/100 gm)</td>
<td>2.7</td>
<td>2.7</td>
<td>3.2</td>
<td>3.2</td>
<td>3.4</td>
<td>3.3</td>
<td>2.9</td>
</tr>
</tbody>
</table>

HR (beats/min) 81 ± 12 115 ± 19* 89 ± 11 76 ± 9 75 ± 12 81 ± 32 87 ± 33 83 ± 27
CVP (torr) 7 ± 1 10 ± 1 9 ± 1 9 ± 1 7 ± 0 6 ± 0.4 6 ± 0.4 6 ± 0.6
BUN 165 ± 1 162 ± 3 156 ± 2 166 ± 2 183 ± 2 6 6 153 ± 1
Na (mEq/L) 155 ± 2 134 ± 1* 139 ± 2 133 ± 6 145 ± 2 141 ± 6 146 ± 6 153 ± 1
K+ (mEq/L) 3.9 ± 0.7 3.5 ± 0.2 3.5 ± 0.2 3.2 ± 0.2 3.8 ± 0.2 3.5 ± 0.3 3.6 ± 0.2 4 ± 0.2
HCT (%) 44 ± 3 33 ± 1* 36 ± 2 42 ± 8 41 ± 4 43 ± 5 42 ± 4 43 ± 5
OSM (mOsm/L) 321 ± 4 351 ± 6* 340 ± 7 336 ± 6 336 ± 6 329 ± 7 —
pH 7.40 ± 0.01 7.33 ± 0.02 7.41 ± 0.01 7.41 ± 0.01 7.36 ± 0.02 7.35 ± 0.02 7.33 ± 0.03
PCO₂ (torr) 30 ± 1 32 ± 1 30 ± 1 30 ± 1 30 ± 1 30 ± 1 30 ± 1 30 ± 1
PO₂ (torr) 142 ± 8 150 ± 8 152 ± 6 154 ± 5 144 ± 8 144 ± 10 149 ± 9 145 ± 6

*p ≤ 0.05, CBF = cerebral blood flow; MAP = mean arterial pressure; CVR = cerebrovascular resistance; HR = heart rate.
curring in rabbits subjected to 15 minutes of total cerebral ischemia, decreases infarct size in cats following middle cerebral artery occlusion, and may prolong the safe permissible time for occlusion of major cerebral arteries during aneurysm surgery. Mannitol has been shown to restore CBF to normal following acute subarachnoid hemorrhage in cats. Persistent resolution of life threatening neurological deficits from vasospasm has been observed following continuous infusion of large doses of mannitol in conjunction with arterial hypertension produced by dopamine. The mechanisms underlying these observations are unknown. It has been hypothesized that the protective action of mannitol results from reduction in swelling of capillary endothelial or perivascular cells, or decreases in pericapillary edema. Alternatively, it has been suggested that the beneficial effects are related to enhanced CBF.

In this study, a bolus of 2 gm/kg of mannitol administered over seven minutes produced a small, transient increase in CBF. However, 30 minutes after completion of mannitol infusion, a significant reduction in CBF below control values was noted and persisted for at least three hours. Previous studies in man and experimental animals using somewhat smaller doses of mannitol or urea demonstrated an increase in CBF of greater magnitude than that reported herein, during or immediately after administration of the bolus, which returned to control levels within 30 minutes. The increase in CBF which occurs after a bolus of mannitol may be explained by one or more of the following. Administration of mannitol results in a transient increase in intravascular volume, cardiac output, and in certain situations an increase in systemic arterial pressure. In normal subjects with intact autoregulation, these factors alone may not increase CBF. However, mannitol is also associated with an increase in CMRO2, an increase in arterial PCO2, hemodilution, and decreased blood viscosity. The reason that the increase in CBF observed in this study was smaller than that reported by others may, at least in part, be due to the efforts we made to compensate for the transient increase in arterial PCO2 which occurred shortly after administration of the mannitol. The increase in PCO2 from mannitol has also been observed in humans undergoing craniotomy but the cause of this change remains obscure. The reduction in CBF and increase in CVR following mannitol has not been previously reported. This decrease in CBF which we observed was approximately 20% and the increase in CVR was of equal proportion and occurred approximately 30 minutes after the mannitol was given and persisted for the duration of the experiment—another 2½ hours. The dose of mannitol used in this study was higher than that customarily used and was associated with a significant diuresis. Urine losses were not replaced and it is possible that the reduction in CBF was related to dehydration, although the cardiovascular, biochemical, and hematological parameters measured remained normal and were not indicative of decreased circulating volume. Alternatively, administration of mannitol as a bolus of 2 gm/kg may have resulted in a transient opening of the blood brain barrier, allowing vasoactive plasma substances to diffuse into the extravascular compartment and constrict the parenchymal vessels.

Acknowledgments

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References

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The effects of high dose mannitol on cerebral blood flow in dogs with normal intracranial pressure.

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