Title: MANNITOL-INDUCED HEMODYNAMIC CHANGES AND THEIR EFFECTS ON INTRACRANIAL HYPERTENSION

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Introduction. Rapid administration of mannitol in individuals with normal intracranial pressure (ICP) causes an initial increase in ICP[1]. In contrast, it has recently been demonstrated that a mannitol bolus rapidly reduces ICP in animals with intracranial hypertension[2]. In both cases, mannitol's initial impact on intracranial pressure has been shown to derive from its vascular rather than its osmotic effects[3]. The present study was conducted to elucidate the relationship between ICP and hemodynamic changes following a rapid infusion of mannitol in humans with raised ICP.

Methods. After obtaining approval from our Hospital Ethics Committee and informed consent from the next of kin, we studied 5 comatose patients (3 women and 2 men), aged 24-68 years, who had been given mannitol for the control of intracranial hypertension. Two of these patients had sustained major head injuries and three had suffered a massive subarachnoid hemorrhage. In all five cases, 0.5 to 1.0g Kg^{-1} doses of a solution of 20% mannitol were infused rapidly over a 5-minute period. ICP was continuously transduced (Ladd M1000 pressure monitor) and recorded (Ladd Medilogic recorder) using the external auditory meatus as the zero reference point. Baseline circulatory data included heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure ($\overline{PAP}$), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). Total peripheral resistance (TPR) and pulmonary vascular resistance (PVR) were calculated in dynes.sec.cm^{-5}. ICP and hemodynamic measurements were recorded 2 minutes, 5 minutes, and 15 minutes after the beginning of the 5-minute infusion. Data were analyzed using Bonferroni's t-test for multiple comparisons. $P<0.05$ was considered to be significant.

Results. Our results appear in Table 1. Data are expressed as the mean + SEM. Fifteen mannitol infusions (2-5 per patient), given during the first 48 hours, were analyzed. Means from each patient were calculated and our data represent mean values of the means (n=5). In all patients, ICP significantly decreased without any initial increase ($P<0.05$). The systemic hemodynamic response to mannitol consisted of an early, statistically significant decrease in TPR which correlated closely with the early decrease in ICP ($P<0.05$). MAP decreased gradually ($P<0.1$). HR remained virtually unchanged. A significant increase in CVP, $\overline{PAP}$, PCWP, and CO ($P<0.05$) correlated with the above changes. The decrease in PVR was not significant ($P<0.2$).

Discussion. Intracranial hypertension eliminates the cerebral vasculature's capacity to autoregulate. Any change in MAP is therefore reflected in ICP[4]. MAP itself is affected by changes in CO and TPR. Mannitol when given rapidly increases CO, decreases peripheral vascular resistance, and reduces blood viscosity. We believe that in patients with increased ICP the initial effect of mannitol on TPR overrode its effect on CO, decreasing MAP and hence ICP. In conclusion, our data support the safety of rapid administration of relatively large doses of mannitol in patients with intracranial hypertension. Furthermore, we suggest that the drug's initial effect derives in large part from hemodynamics.

References.

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TABLE 1 : Mean changes in ICP (mmHg), MAP (mmHg), HR (beats/min), CVP (mmHg), $\overline{PAP}$ (mmHg), CO (L/min), TPR (dynes. sec.cm-5),and PVR (dynes.sec.cm-5) ± SEM (n=5)

	Baseline	2 minutes of Infusion	End of Infusion	10 minutes post-infusion
ICP	31.6±1.5	26.5±1.3*	18.9±0.6*	13.8±1.0*
MAP	104.0±2.8	98.2±3.3	97.2±3.4	95.2±2.1
HR	70.2±3.9	69.5±3.6	72.3±3.9	72.7±3.7
CVP	7.9±0.7	10.2±0.8	11.6±0.6*	9.8±0.8
$\overline{PAP}$	17.1±1.1	19.8±1.2	22.2±1.3*	20.1±1.3
PCWP	10.6±1.0	13.9±1.2	14.8±1.1*	12.8±1.0
CO	5.2±0.6	7.6±0.9	8.7±0.8*	6.7±0.8
TPR	1606±177	1006±111*	822±75*	1118±118
PVR	103±13	69±10	73±9	96±12

*P< 0.05