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Research Report

Real-time hemodynamic response and mitochondrial function changes with intracarotid mannitol injection

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ABSTRACT

Disruption of blood brain barrier (BBB) is used to enhance chemotherapeutic drug delivery. The purpose of this study was to understand the time course of hemodynamic and metabolic response to intraarterial (IA) mannitol infusions in order to optimize the delivery of drugs for treating brain tumors. *Principal results*: We compared hemodynamic response, EEG changes, and mitochondrial function as judged by relative changes in tissue NADH concentrations, after intracarotid (IC) infusion of equal volumes of normal saline and mannitol in our rabbit IC drug delivery model. We observed significantly greater, though transient, hyperemic response to IC infusion of mannitol compared to normal saline. Infusion of mannitol also resulted in a greater increase in tissue NADH concentrations relative to the baseline. These hemodynamic, and metabolic changes returned to baseline within 5 min of mannitol injection. *Conclusion*: Significant, though transient, changes in blood flow and brain metabolism occur with IA mannitol infusion. The observed transient hyperemia would suggest that intravenous (IV) chemotherapy should be administered either just before, or concurrent with IA mannitol injections. On the other hand, IA chemotherapy should be delayed until the peak hyperemic response has subsided.

1. Introduction

Regional blood flow profoundly affects the delivery of intraarterial (IA) drugs in pharmacokinetic and experimental models (Dedrick, 1988; Joshi et al., 2006, 2008a, 2008b). While an increase in cerebral blood flow (CBF) will improve the deposition of concurrently injected intravenous (IV) drugs to the brain tissue, it will adversely affect the delivery of IA drugs. In theory, any increase in CBF will increase the amount of IV drug delivered due to the proportional increase in CBF. To the contrary, an increase in CBF, will dilute the IA drugs, decrease the transit time, and increase regional clearance, so as to adversely affect the regional deposition of IA drugs. IA mannitol is used for the disruption of the blood brain barrier (BBB) to facilitate delivery of

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Table 1 – Physiological changes during intracarotid injection of normal saline and mannitol.

	Challenge	Baseline	Peak injection	1 min	3 min	5 min	10 min
Temperature (°C)	*Saline*	37.1±0.9	37.1±0.9	37.1±0.9	37.2±0.8	37.1±0.8	36.9±0.9
	Mannitol	36.7±0.7	36.7±0.7	36.7±0.7	36.8±0.8	36.8±0.8	36.8±0.5
Resp. rate (breaths/min)	*Saline*	62±8	62±8	62±8	62±8	62±8	62±8
	Mannitol	62±8	62±8	62±8	62±8	62±8	62±8
Heart rate, (beats/min)	*Saline*	263±19	265±19	262±8[a]	268±22	264±10	255±20
	Mannitol	250±21	252±36	246±16	253±10	263±29	267±27
MAP (mmHg)	*Saline*	63±18	95±13[b,f]	79±17[c]	66±17[a,c,d]	59±17[c,d,e]	60±19[c,d,e]
	Mannitol	65±21	97±13[b]	73±19[c]	88±14[b,d]	75±19[d]	60±18[c,d,e]
% ΔLDI	*Saline*	100±0	13±5[b,f]	237±90[b,c]	99±11[c,d,e]	109±13[c,d,e]	107±34[c,d,e]
	Mannitol	100±0	11±6[a,f]	234±112[b,c]	140±38[c,d,e]	118±29[c,d,e]	87±17[c,d,e]
% ΔLDC	*Saline*	100±0	37±20[a,b]	201±82[b,c]	120±42[c,d]	139±88[c]	139±11[c]
	Mannitol	100±0	20±11[b]	252±207[c]	139±44	127±46	97±41[d]
$EtCO_2$, (mmHg)	*Saline*	21±4	22±4	21±5	22±4	21±1	21±1
	Mannitol	22±3	23±4	23±4	22±3	22±3	22±3
EEG score	*Saline*	4±1	1±1[b,f]	3±1[b,c]	4±1[a,c,e]	4±1[c,e]	4±1[c,e]
	Mannitol	4±1	1±1[a,f]	2±1[b,c]	3±1[c,e]	4±1[c,e]	4±1[c,e]
NADH (AU)	*Saline*	0±0.00	0.7±0.26[a,b,f]	0.05±0.16[c]	0.03±0.05[c]	0.02±0.05[c]	0.01±0.05[c]
	Mannitol	0±0.02	1.05±0.37[b,f]	0.09±0.15[c]	0±0.1[c]	0±0.1[c]	0.01±0.05[c]

Abbreviations: $EtCO_2$: end-tidal carbon dioxide tension; MAP: mean arterial pressure; % ΔLDI: %-change in laser doppler blood flow from baseline on the side of mannitol infusion; % ΔLDC: %-change in laser doppler blood flow from baseline on the contralateral side; EEG score: electroencephalographic score 0-5 on standardized scale; NADH: nicotinamide adenine dinucleotide; AU: arbitrary units.
[a] Significant difference between mannitol and saline ($P<0.05$), Significant difference between repeat measure ($P<0.0033$).
[b] From base.
[c] From peak.
[d] From 1 min.
[e] From 3 min.
[f] From 5 min.

chemotherapeutic drugs (Neuwelt et al., 2008; Riina et al., 2009; Shin et al., 2012). The dose of mannitol for this purpose should be sufficient to displace blood and dehydrate endothelial cells for approximately 30–40 s (Bellavance et al., 2008; Rapoport, 2000), for rabbits it is 8 ml over 30–40 s (Perkins and Strausbaugh, 1983; Wang et al., 2007). Several investigators have reported significant hemodynamic effects such as changes in cardiac output, systemic vascular resistance, hypertension, increased CBF, and increased ICP during BBB disruption (Doolittle et al., 2000; Gumerlock et al., 1994; Hardebo and Nilsson, 1980; Hiesmayr et al., 1987; Marchi et al., 2007). The purpose of this study was to understand the time course of hemodynamic and metabolic response to intraarterial (IA) mannitol infusions in order to help optimize the delivery of drugs for treating brain tumors.

In this report we describe the real-time hemodynamic effects of infusion of 25% mannitol compared to normal saline infusions, in doses that are used for the disruption of BBB in our IA drug delivery model using New Zealand white rabbits. To our best knowledge only a few studies have addressed the temporal hemodynamic and metabolic changes after IA mannitol injections and most of these studies have assessed blood flow or metabolism at specific time points, not continuously (Chi et al., 1991, 2013; Hardebo and Nilsson, 1980; Hiesmayr et al., 1987). To assess changes in mitochondrial function, we monitored tissue nicotinamide adenine dinucleotide (NADH) levels using ultraviolet spectroscopy, that assesses tissue redox state in real-time and provides a marker of cerebral ischemia(Mayevsky and Rogatsky, 2007). To rule out that the observed increase in NADH levels during mannitol and saline injections was not due to the displacement of hemoglobin that could unmask tissue fluorescence, we conducted a further dose response study with IA NADH.[1]

2. Results

2.1. *Comparison of response to IA saline vs. IA mannitol*

Comparison between saline and mannitol challenges was undertaken in New Zealand white rabbits ($n=9$). Baseline hemodynamics and end-tidal CO_2 were comparable between the two challenges, Table 1. Infusion of both, saline or mannitol, resulted in an initial increase in mean arterial pressure, and decrease in CBF, with rebound increase that was more sustained with mannitol. Greater hemodynamic instability was seen with mannitol as compared to saline, Fig. 2. The increase in mean arterial pressure (MAP) with mannitol was often transient and immediately followed by a decrease and then a second increase in MAP, as shown in Fig. 3A and B. The decrease in MAP coincided with a slight difference in heart rates (262±8 bpm baseline to 246±16 bpm at 1 min, $P=0.016$), which was significant between the two challenges. However with mannitol there was a secondary increase in MAP at 3 min with a corresponding hyperemic response that was significantly different from saline injections, 88±14 vs. 66±17 mm Hg, $P=0.001$.

[1]IC: intracarotid, IA: intra-arterial; BBB: blood brain barrier; NADH: nicotinamide adenine dinucleotide; CBF: cerebral blood flow; MAP: mean arterial pressure (MAP); A/D: analog-to-digital.