Title: ETHANOL ENHANCES ENLARGEMENT OF INTRACRANIAL FOCAL ISCHEMIC LESIONS

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Introduction. The relationship of ethanol (ETOH) to CNS trauma has frequently been noted, especially as a causative factor contributing to more than half the deaths in vehicular accidents in the U.S.A. Previous studies [1,2] have shown ethanol potentiation of experimental CNS injury using toxic ETOH levels, without determining lesion volumes and without delineating the relationship of lesion size to changes in cerebral perfusion pressure. In previous studies we have developed a standardized experimental model for creating pressure induced intracranial focal ischemia (PIFI)[3,4] in which neurobehavioral and physiopathological responses are quantified. Using the PIFI model, we will evaluate neurobehavioral and physiopathological responses after ethanol infusion under normotensive and hypotensive conditions.

Method. Under pentobarbital anesthesia, canines were intubated and ventilated so as to achieve normoxia and normocarbia; instrumented with appropriate catheters and electrodes to monitor mean arterial blood pressure (MAP), central venous pressure (CVP), heart rate, temperature, ECG and blood gases; and randomly assigned to one of 5 groups: 1 - Normotension, PIFI; 2 - Normotension, ETOH 1 hr., followed by PIFI; 3 - ETOH, hypotension, no PIFI; 4 - Hypotension, PIFI; 5 - ETOH 1 hr, Hypotension and PIFI. Induced hypotension targeted a MAP of 50 torr using an infusion of trimetaphan. PIFI was produced by placement of a 9/16" De Martel retractor on the right somatosensory cortex for one hour at a retraction pressure of 30 torr using an electronic pressure sensitive retractor sheath. Ethanol was infused over a period of an hour to achieve a blood level between 150 and 200 mg%. Serum ETOH levels were monitored at 15 min intervals after start of infusion using a dichromate assay method. Upon termination of the experiment, the animals were evaluated using a neurobehavioral scale (NBS) with 0=death before 7 days; 1=paralysis; 2=not paralyzed but unable to stand; 3=standing with weakness; 4=normal standing and walking. The animals were sacrificed at one week, the brains taken from all animals upon demise and fixed in formaldehyde for 2 weeks. The brains were sectioned transversely in 1 cm slices and a lesion volume profile calculated planimetrically. Cerebral perfusion pressure (CPP) was calculated as the MAP-CVP or BRP, whichever was highest. Students "t" test was used to determine significance of changes in lesion volumes between groups.

Results. No significant differences could be noted between any of the groups in pH, PAO_2, $PACO_2$ and temperature during the experiments. The most striking differences (Fig. 1) could be noted in the lesion volume of the normotensive, ETOH, 30 torr brain retraction pressure (BRP) PIFI (Group 2) compared against its control in Group 1 ($p=<0.01$) and in the lesion volume of the ETOH, Hypotension, 30 torr PIFI (Group 5) compared to a control (Group 4) without ethanol ($p=<0.01$). While 3 animals in Group 4 survived longer than 7 days, there were no survivors in Group 5.

Discussion. This study may have clinical relevance since the PIFI model has histological characteristics similar to that found in trauma and because the ETOH levels maintained for one hour prior to PIFI is well within the legal "intoxication" range (>150 mg %). In both the normotensive and hypotensive ETOH PIFI groups, a five fold increase in lesion volume occurred when compared to the non alcoholic controls. Reducing the MAP using induced hypotension may be similar clinically to head trauma with an associated injury and hypovolemia. The mechanism for lesion enhancement with ETOH may be in the formation of lipid free radicals. It is possible that the production of the metabolite acetaldehyde from ETOH increases the free radical pool in the area of injury causing a depletion of aqueous antioxidants with marked membrane lipid destruction. (Supported in part by a grant from the Distilled Spirits Council.)

References.

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Group	No. Animals	MAP torr	CPP torr	CVP torr	BRP torr	ETOH mg%	Lesion Vol. cc.	NBS
1. Normotension, PIFI	5	131±4	101±5	3.0±0	30	0	0.8±0.8*	3.5
2. Normotension, ETOH, PIFI	5	145±3	115±4	7.0±0	30	196±9	4.5±1.8*	4.0
3. ETOH, Hypotension	3	62±2	58±3	5.0±1	0	203±10	0	4.0
4. Hypotension, PIFI	5	53±2	24±2	4.0±.7	30	0	2.9±1.0§	1.0
5. ETOH, Hypotension, PIFI	4	53±1	24±1	3.0±1	30	168±6	14.9±6.9§	0

Fig. 1. Lesion volumes, ETOH levels, brain retraction pressures, neruobehavioral rating, MAP, CVP and CPP in 5 experimental groups.

* $p= < 0.01$ § $p= < 0.01$

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