FUROSEMIDE REDUCES BRAIN WATER IN CEREBRAL INJURY IN DOGS

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Introduction: Furosemide, a sulfonamide diuretic, is often used to lower increased intracranial pressure following head injury in man. The mechanism of action of furosemide in decreasing intracranial pressure may be mediated by diuresis and the subsequent development of an osmotic transfer of water from the brain. No definite evidence for this mechanism has been shown in brain injury.[1,2] We determined the effects of furosemide on brain water in dogs with cerebral cold injury, with and without renal function.

Methods: Thirty mongrel dogs of both sexes weighing 10 to 20 kgs (mean 18.7 kgs ± 4.8) were induced with a single intravenous dose of sodium thiopental (20 mg/kg) and intubated. Anesthesia was maintained with 70% N_2O in O_2 supplemented with morphine 1.0 mg/kg and curare 0.3 mg/kg intravenously initially and repeated as necessary. The animals were ventilated to maintain normocapnia ($PaCO_2$=40.4 torr ± 4.3). End-tidal CO_2 and N_2O were monitored with a mass spectrometer (Perkin-Elmer 1100). An arterial catheter was placed through a femoral cutdown and arterial pressure continuously recorded. Intracranial pressure was continuously monitored with a subarachnoid bolt placed on the same side as the lesion. A cold lesion was produced on one cerebral hemisphere by the 5 minute application of liquid nitrogen to a 27 mm diameter area of the exposed skull. A laparotomy was then performed to cannulate the urinary bladder and isolate both renal vascular pedicles. The dogs were then randomized into four groups: (1) sham (normal saline 0.1 cc/kg IV and the laparotomy closed); (2) furosemide (furosemide 1 mg/kg IV and the laparotomy closed); (3) nephrectomy (normal saline 0.1 cc/kg IV, the renal pedicles ligated, and the laparotomy closed); (4) both (furosemide 1 mg/kg IV, the renal pedicles ligated and the laparotomy closed). The dogs were monitored for 270 minutes after the cold lesion was produced and then terminated with intravenous barbiturates. Samples of brain were obtained from the damaged area and from the analogous area in the opposite undamaged cortex and weighed (wet weight). Mean sample weight was 1.379 grams ± 0.363. Samples were then placed in an oven desiccator for seven days until a difference of 0.5 milligrams or less was obtained on two consecutive weighings (dry weight). The percent of brain weight as water was calculated as follows:

$$\frac{(\text{wet wt}) - (\text{dry wt})}{(\text{wet wt})} \times 100 = \%\ \text{weight as}\ H_2O$$

The data were analyzed using t-tests; a P value of 0.05 was considered significant.

Results: Intracranial pressure increased with liquid nitrogen application from 9 ± 3 SD to 35 ± 16 SD in 30 minutes and remained elevated for the duration of the study regardless of treatment. In those dogs receiving furosemide with intact kidneys, diuresis began within 30 minutes of injection. The brain weight data are presented in the table. The damaged area contained more water than normal brain regardless of treatment. Furosemide coupled with normal renal function significantly decreased brain water when compared with the sham group in both normal and damaged brain. In nephrectomized dogs, furosemide failed to significantly decrease the water content of normal or damaged brain as compared with the sham group (P=.24 & P=0.7).

Conclusion: Our data indicate that furosemide decreases the water content of normal brain in dogs with contralateral cerebral cold injury. No significant decrease in water content of normal brain occurred in nephrectomized animals; therefore, this effect appears to be mediated by diuresis. Furosemide also significantly decreased brain water in the damaged areas. Such an effect may represent an advantage in the treatment of intracranial pressure over such drugs as mannitol or glycerol which have been shown to decrease water content of normal brain only.[3]

	% Brain Weight (mean ± SEM)	
	Normal	Damaged
Sham (N=8)	76.2% ± 0.4	79.3% ± 0.6*
Furosemide (N=6)	74.8% ± 0.4+	77.6% ± 0.7*+
Nephrectomy (N=8)	75.5% ± 0.5	77.9% ± 0.6*
Furosemide + Nephrectomy (N=8)	75.4% ± 0.3	77.9% ± 0.3*

*P < .01 Damaged Versus Normal Brain Within Groups (paired t-test)
+P = .03 Furosemide Alone Versus Sham Group (unpaired t-test)

References:
(1) Gaab M, Knoblich OE, Schupp J, et al: Effect of Furosemide (Lasix) on Acute Severe Experimental Cerebral Edema. J Neurol 220:185-197, 1979
(2) Buhrley LE, Reed DJ: The Effect of Furosemide on Sodium-22 Uptake Into Cerebrospinal Fluid and Brain. Exp Brain Res 14:503-510, 1972
(3) Fishman RA: Brain Edema. N Eng J Med 293:(14)706-711, 1975