

Influence of Mannitol and Furosemide, Alone and in Combination, on Brain Water Content after Fluid Percussion Injury

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Background: Furosemide and mannitol are used to reduce intracranial pressure, but the impact of furosemide on edema of injured brain is unclear. The authors examined the effects of furosemide and mannitol, alone and in combination, on brain water content in brain-injured rats.

Methods: Anesthetized rats were subjected to a 2.2-atm left hemispheric fluid percussion injury. Two and three-quarters hours later, animals received 0.5, 1, 4, or 8 g/kg mannitol; 8 mg/kg furosemide; a combination of 4 g/kg mannitol plus 4 mg/kg furosemide; or 8 g/kg mannitol plus 8 mg/kg furosemide. One hour later (4 h after injury), plasma osmolality was measured, and hemispheric water content was determined by drying. Other animals were subjected to injury without drug treatment (impact only) or did not undergo injury (control). Pairwise group comparisons regarding the effects of mannitol and furosemide were restricted to only four groups: impact only, 8 g/kg mannitol, 8 mg/kg furosemide, and 8 g/kg mannitol plus 8 mg/kg furosemide.

Results: The water content of both hemispheres in the impact-only group was greater than in the control group (left greater than right). Mannitol, 8 g/kg, increased osmolality from 306 ± 4 to 351 ± 6 mOsm/kg (mean \pm SD) and reduced water content in the left hemisphere from $80.06 \pm 0.84\%$ (impact only) to $78.24 \pm 0.73\%$. Furosemide, 8 mg/kg, had no effect on osmolality or water content. Brain water in animals treated with 8 g/kg mannitol plus 8 mg/kg furosemide did not differ from that seen with 8 g/kg mannitol alone.

Conclusions: Mannitol increased plasma osmolality and reduced water content of the injured and contralateral hemispheres, whereas the authors observed no effect of furosemide when given either alone or in combination with mannitol.

THE ability of mannitol to reduce intracranial pressure (ICP) is well established. Its principal mechanism of action is to increase plasma osmolality, resulting in water movement out of the brain along the osmotic gradient.^{1,2} Furosemide, alone or in combination with mannitol, is also used to reduce ICP.³⁻⁵ However, despite decades of experimentation, the mechanism by which furosemide reduces ICP is not well understood. Furosemide can reduce cerebrospinal fluid (CSF) production, but typically only when given in doses much higher than those used clinically.^{6,7} Studies on the effects of furosemide on brain water content have been inconsistent; some have

shown no drug-induced reductions in water content,⁸⁻¹¹ whereas others have shown reductions in edema.¹²⁻¹⁵

We recently examined the effects of varying doses of mannitol and furosemide, alone and in combination, on brain water content of normal rats.¹⁶ As expected, mannitol increased plasma osmolality and reduced water content. Furosemide alone had no effect on normal brain water or plasma osmolality. The only unique effect of the combination of mannitol and furosemide was a greater increase in plasma osmolality and an associated greater reduction of brain water content than achieved with mannitol alone. However, because these experiments were performed in normal animals, the current experiments were designed to extend our earlier observations using a model of brain injury with preexisting edema.

Materials and Methods

All procedures were approved by the University of Iowa Animal Care and Use Committee, Iowa City, Iowa. Male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing 302 ± 32 g (mean \pm SD) were anesthetized with 4% halothane in 100% oxygen in a plastic box. When the rats were unresponsive, a tracheotomy was performed, and a tracheostomy tube was inserted. Animals were subsequently ventilated with an inspired gas mixture of 1-1.5% halothane in 40-50% O₂-balance N₂. Femoral arterial and venous catheters (PE-50) were inserted. Mean arterial pressure (MAP) was continuously measured from the femoral artery. Rectal temperature was maintained at 37°C with a heating pad. After preparation, arterial pH, partial pressure of oxygen, and partial pressure of carbon dioxide were measured, and ventilator settings were adjusted to achieve normocapnia.

Animals were turned prone. The scalp was incised in the midline and reflected laterally. A 5-mm-diameter circular burr hole was drilled in the left side of the calvarium with a small trephine (Fine Science Tools, North Vancouver, British Columbia, Canada). The hole was located midway between the coronal and lambdoid sutures and was centered approximately 2.5-3.0 mm lateral to the midline. The dura remained intact. The hub of a standard 20-gauge blunt needle (Becton, Dickinson and Co., Franklin Lakes, NJ) was machined to fit snugly into the burr hole. The hub was then fixed in place with cyanoacrylate glue.

When preparation was complete, the hub was filled

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with normal saline and attached to the outlet port of a fluid percussion unit (manufactured by the Department of Bioengineering, Virginia Commonwealth University, Richmond, VA). With the animal still prone, a 2.2-atm peak pressure pulse lasting 20–30 ms was delivered to the animal. The pressure generated during the pulse was monitored with an oscilloscope; animals were excluded if peak pressures were inadequate. Anesthesia, mechanical ventilation, and normothermia were maintained thereafter. Catheters were intermittently flushed with small volumes of heparinized saline, and any blood withdrawn was replaced with an equal volume of saline. No other fluids were infused.

Two and one-half hours after injury, animals were assigned in random sequence to one of nine groups. Arterial blood was sampled for the measurement of arterial oxygen tension, arterial carbon dioxide tension, pH, and plasma osmolality (freezing point depression, Advanced Instruments model 3MO; Needham Heights, MA). Beginning 2.75 h after injury, the selected drug or drugs were infused into the femoral venous catheter at a constant rate over 15 min using a syringe pump. The groups were as follows (group sizes can be found in table 1):

Control: Animals were prepared as above, including placement of the fluid percussion cannula. No fluid percussion injury was performed, and no drug infusions were administered.

Impact only: Fluid percussion injury and ventilatory support were performed, but no drugs were infused.

0.5, 1, 4, or 8 g/kg mannitol: A solution of 25 g mannitol/100 ml (in water) was used without dilution. This resulted in the infusion of approximately 0.6, 1.2, 4.8, or 9.6 ml of fluid for the four doses, respectively.

8 mg/kg furosemide: A solution of 10 mg furosemide/ml was used. This resulted in an infusion of approximately 0.24 ml of drug to a 300-g animal.

4 g/kg mannitol plus 4 mg/kg furosemide: Both drugs were combined in the same syringe.

8 g/kg mannitol plus 8 mg/kg furosemide: Both drugs were combined in the same syringe.

All drug infusions were complete by 3 h after injury. One hour later, arterial blood gases, pH, and plasma osmolality were again measured. The animals were killed with an overdose of halothane and decapitated, and the brain was rapidly removed. The cerebellum and brain stem were removed. The cerebral hemispheres were then separated, placed into preweighed glass vials, weighed to the nearest 0.1 mg, dried at 80°C for 3 days, and reweighed. Brain water content was calculated as the wet-dry difference and expressed as % water [$= ((\text{wet weight} - \text{dry weight})/\text{wet weight}) \times 100$].

Data Analysis and Statistics

All results are expressed as mean \pm SD.

For the purpose of maintaining statistical power when comparing the effects of mannitol, furosemide, and their combinations, only selected intergroup comparisons were performed. The primary purpose of the study was to compare the effects on brain water content of high doses of mannitol and furosemide, alone and in combination. First, to verify that impact resulted in an increase in water content, water content of both hemispheres for control and impact-only groups were compared with a repeated-measures analysis of variance, with left and right hemispheric water contents as the repeated measure; a *post hoc* paired *t* test was used to examine left *versus* right hemispheric water content. Second, a two-way repeated-measures analysis of variance (with left *vs.* right hemisphere as the within-group factor) was used to examine the role of mannitol and furosemide. To maintain statistical power, the analysis was limited to the impact-only, 8 g/kg mannitol, 8 mg/kg furosemide, and 8 g/kg mannitol plus 8 mg/kg furosemide groups. Differences in MAP, arterial blood gases, and osmolality were examined using two-way repeated-measures analysis of variance (with group as the between-group factor and values measured before and after drug administration as the repeated measure). *Post hoc* testing was performed using a Scheffé test.

An initial examination of brain water content between the groups indicated no unique treatment \times hemisphere effect (although water content in the injured left hemisphere was always greater than in the right hemisphere, regardless of group). Subsequently, a one-way analysis of variance was used to examine intergroup differences in left hemispheric water content.

Results

A total of 108 rats were subjected to fluid percussion injury or served as controls. Twelve injured animals died before the end of the experiment. Protocol errors or errors in tissue handling or blood sampling occurred in 5 animals, leaving 91 animals for which osmolality and brain water data were available.

Blood pressure, blood gases, osmolality, and hemispheric brain water content data for all groups are presented in table 1.

Injury resulted in an increase in water content in both hemispheres (control *vs.* impact only), although water content was always greater in the left hemisphere (paired *t* test within each group, $P = 0.02$ – 0.0001).

As expected, mannitol resulted in a dose-related increase in osmolality ($P < 0.0001$, analysis of variance containing all four mannitol doses plus impact only). Similarly, there was a dose-related decrease in brain water content (both hemispheres, $P < 0.0001$).

Table 1. Summary Data, All Groups

	Control (No Impact)	Impact Only	0.5 g/ml Mannitol	1 g/kg Mannitol	4 g/kg Mannitol	8 g/kg Mannitol	8 mg/kg Furosemide	4 g/kg Mannitol + 4 mg/kg Furosemide	8 g/kg Mannitol + 8 mg/kg Furosemide
n	12	10	4	9	12	10	11	11	12
MAP, mmHg									
Baseline	99 ± 11	95 ± 12	103 ± 13	98 ± 14	90 ± 11	98 ± 12	94 ± 13	91 ± 12	97 ± 10
End	100 ± 9	96 ± 16	103 ± 23	94 ± 13	93 ± 12	83 ± 10*	88 ± 10	84 ± 13	78 ± 17*
PaO ₂ , mmHg									
Baseline	283 ± 54	332 ± 50	353 ± 33	282 ± 45	301 ± 68	306 ± 53	314 ± 63	327 ± 38	319 ± 39
End	272 ± 55	327 ± 57	360 ± 51	292 ± 43	327 ± 101	285 ± 116	310 ± 80	379 ± 51	331 ± 102
Paco ₂ , mmHg									
Baseline	35 ± 3	37 ± 4	36 ± 5	38 ± 5	36 ± 5	36 ± 5	37 ± 4	34 ± 4	36 ± 4
End	36 ± 5	38 ± 3	32 ± 10	35 ± 4	35 ± 7	35 ± 7	33 ± 4	33 ± 5	36 ± 4
pH									
Baseline	7.41 ± 0.03	7.41 ± 0.03	7.41 ± 0.01	7.40 ± 0.04	7.40 ± 0.04	7.41 ± 0.04	7.38 ± 0.02	7.42 ± 0.03	7.39 ± 0.04
End	7.41 ± 0.02	7.41 ± 0.03	7.43 ± 0.04	7.41 ± 0.04	7.39 ± 0.06	7.36 ± 0.10	7.44 ± 0.02	7.44 ± 0.04	7.31 ± 0.16*
Osmolality, mOsm/kg									
Baseline	304 ± 5	307 ± 4	303 ± 5	305 ± 5	307 ± 7	306 ± 4	308 ± 5	306 ± 4	305 ± 4
End	305 ± 7	306 ± 6	306 ± 3	308 ± 6	327 ± 9	351 ± 6*	308 ± 4	329 ± 10	353 ± 11*
Brain water, % H ₂ O									
Left hemisphere	79.26 ± 0.57	80.06 ± 0.84	79.95 ± 0.27	79.87 ± 0.46	79.13 ± 0.66	78.24 ± 0.73†	79.92 ± 0.68	78.94 ± 0.69	77.95 ± 0.50†
Right hemisphere	78.66 ± 0.61	79.18 ± 1.12	78.72 ± 0.25	78.93 ± 0.78	78.17 ± 0.70	77.27 ± 0.98†	78.87 ± 0.67	78.00 ± 1.03	76.55 ± 0.58†

All values are mean ± SD. Values in the rows titled Baseline were obtained just before drug treatment (approximately 2.75 h after injury), whereas those in the rows titled End were obtained just before the animal was killed (1 h after drug administration). To maintain statistical power, between-groups comparisons were performed only on data in the columns containing **bold** numbers.

For mean arterial pressure (MAP), blood gases, and osmolality, * indicates a statistically significant change as compared with baseline values within a given group. For brain water values, † indicates a significant differences in water content vs. impact-only and 8 mg/kg furosemide animals. In all cases, left hemispheric water content was significantly greater than that of the right hemisphere ($P < 0.02$ – 0.0001 by simple paired t test).

Paco₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension.

There were no differences in pH, arterial blood gas values, plasma osmolality, or MAP before drug treatment in the four selected groups. Statistically significant reductions in MAP and pH (both *vs.* baseline within the groups and *vs.* impact-only animals) were seen in the 8 g/kg mannitol and 8 g/kg mannitol plus 8 mg/kg furosemide groups. There were significant increases in plasma osmolality in both of the groups given 8 g/kg mannitol (both *vs.* baseline measurements within the group and *vs.* impact-only animals). Furosemide alone did not alter plasma osmolality or brain water content (*vs.* impact only). Both 8 g/kg mannitol and the combination of 8 g/kg mannitol plus 8 mg/kg furosemide resulted in a significant decrease in water content *versus* impact only (both hemispheres). There were, however, no differences in osmolality or brain water content *between* these latter two groups. These results are summarized in figure 1.

Discussion

The effects of hypertonic solutions on brain volume and ICP in animals were first described in the early part of the 20th century.^{17,18} Elevated ICP was sporadically treated with hypertonic saline and magnesium solutions

in the 1920s and 1930s,^{19,20} whereas hypertonic glucose was used through the 1950s.^{21–23} Urea, the first widely accepted osmotic diuretic, was introduced by Javid and Settlage in 1956.²⁴ Mannitol was first used in 1961,^{25,26} and since that time, numerous studies have demonstrated the ability of mannitol to reduce brain water content, ICP, and brain bulk. Although a variety of “non-osmotic” mechanisms have been proposed,²⁷ the linear relation between mannitol-induced changes in plasma osmolality and brain water content suggest that the generation of a blood–brain osmotic gradient is the most important mechanism of action.^{1,28}

The effects of furosemide on ICP were first reported in the late 1960s.²⁹ Since then, multiple studies have demonstrated the ability of furosemide to reduce ICP in animals and humans.^{3,12,13,30–32} However, the mechanism of action is much less clear than that for mannitol. Some experiments have suggested an effect of furosemide on brain water content, whereas others have not demonstrated such changes.^{8,11,16,33} Furosemide reduces CSF production, possibly by inhibiting carbonic anhydrase.^{6,34,35} However, one study has reported a CSF-related effect with clinically reasonable doses (*e.g.*, 3–5 mg/kg)⁷; the remaining reports have used much higher doses (20–50 mg/kg).

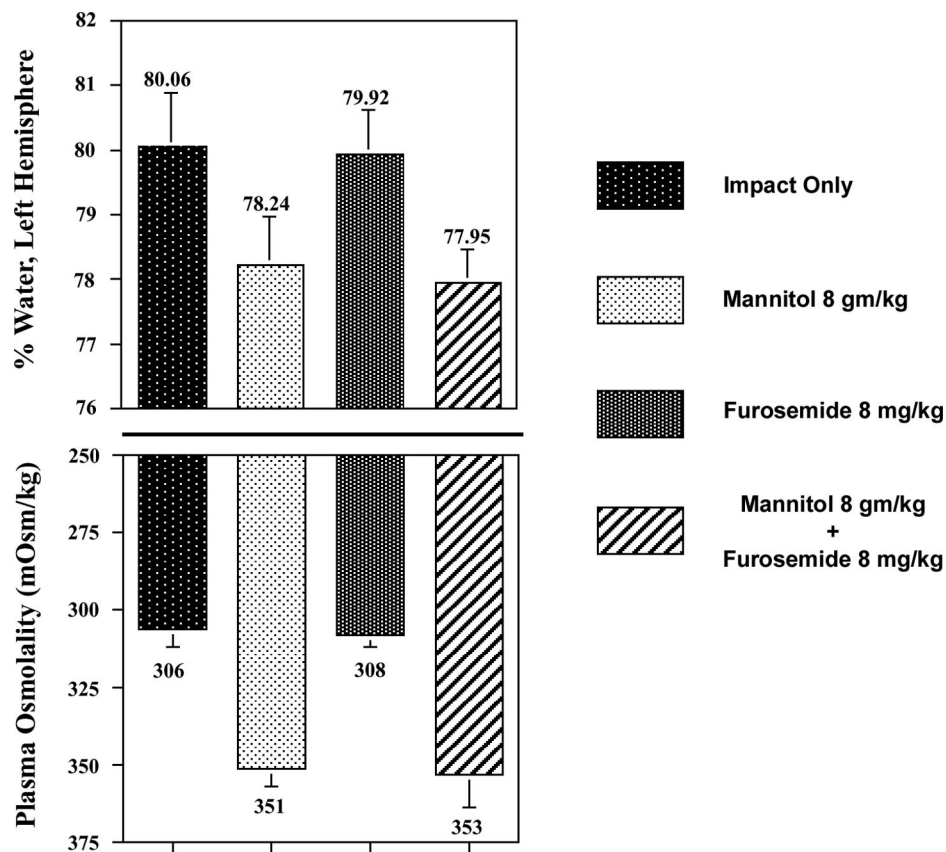


Fig. 1. Water content (% water) for the lesioned left hemisphere (top) and osmolality (bottom) for the four groups used in the primary analysis. All values are mean \pm SD. Mannitol, 8 g/kg, and the combination of 8 g/kg mannitol plus 8 mg/kg furosemide significantly reduced water content and increased osmolality as compared with impact-only animals and *versus* 8 mg/kg furosemide alone (which did not differ from impact only). However, there was no difference between mannitol and mannitol-plus-furosemide groups (in either water content or osmolality).

Therapy with a combination of mannitol and furosemide was first described by Harbaugh *et al.* in 1979.⁹ They demonstrated a reduction of ICP in rabbits subjected to a cortical freezing injury but did not demonstrate an advantage of the combination as compared with mannitol alone, nor did they show an effect on water content. Four subsequent animal studies have also examined the impact of such a combination on ICP.^{4,5,10,36,37} Again, although these studies showed that the combination can reduce ICP, most did not measure brain water. Nevertheless, the combination of mannitol and furosemide was reported to produce a greater increase in serum osmolality than mannitol alone,³⁸ and several studies showed that the combination resulted in a longer lasting reduction in ICP than did mannitol alone.^{4,5,37}

The uncertainty raised by these studies, along with the clinical use of the combination of mannitol and furosemide, led to our earlier study.¹⁶ In that experiment, various doses of mannitol and furosemide, alone or in combination, were administered to normal rats. Mannitol produced the expected dose-related reduction in brain water content, whereas furosemide alone, even in a dose of 8 mg/kg, had no effect on either osmolality or

brain water content. The results suggested that a combination of 8 g/kg mannitol and 8 mg/kg furosemide resulted in a significantly greater reduction in brain water content than was achieved with 8 g/kg mannitol alone, but further analysis indicated that this effect was due entirely to a greater increase in plasma osmolality in the combination group.

To further understand the action of these drugs, we extended our earlier study using animals that had been subjected to a fluid percussion brain injury.³⁹⁻⁴¹ A 2.2-atm injury resulted in an increase in brain water, greater in the directly injured hemisphere. As in normal animals from our previous work, mannitol resulted in a dose-related decrease in water content in both hemispheres, whereas furosemide alone was without effect. In contrast to our previous study, the combination of mannitol and furosemide had no greater effect on plasma osmolality or brain water content than mannitol alone.

Some studies based on focal freezing injuries to the brain have suggested that increasing plasma osmolality does not remove water from injured brain.^{28,42} This lack of effect presumably results from the marked increase in blood-brain barrier permeability produced by cortical freezing and the consequent inability to establish an

osmotic gradient between blood and tissue. In the current study, there was a clear dose–response relation for animals given different doses of mannitol alone and a strong linear relation between osmolality and brain water content (not shown). In addition, there was no obvious difference in the slope of these regression lines for the left and right hemispheres. This suggests that the blood–brain barrier is at least partially intact and that the reflection coefficient did not differ between the hemispheres.

There are a number of limitations to this study. Previous laboratory studies of furosemide and edema have used a variety of injury models, such as cortical freeze lesions, epidural balloons, or cytotoxic compounds. These can all be criticized as producing changes quite different from the edema seen in clinical head injury or brain tumors. Although we used the widely accepted fluid percussion injury model, this also does not perfectly reproduce clinical injury or tumor. Our study was also conducted with very large doses of mannitol and furosemide, doses much larger than used clinically. As discussed in our previous report,¹⁶ pilot experiments did not demonstrate consistent elevations in plasma osmolality or reductions in normal brain water content with smaller doses of mannitol. We hence selected doses to produce consistently measurable increases in plasma osmolality and decreases in brain water within the time frame of our experiments, not to develop clinical treatment protocols. We similarly selected a supraclinical furosemide dose largely to maximize our chances of being able to detect any effect that might be present. We believe that in the face of our inability to demonstrate an effect of furosemide at these high doses, it is unlikely that meaningful changes would be present at lower doses. It should be noted that given the available drug preparations, the administration of mannitol required the infusion of relatively large amounts of fluid (e.g., nearly 10 ml for the highest dose), particularly compared with furosemide (approximately 0.25 ml). This is consistent with clinical practice but may theoretically influence our results. For example, the initial volume expansion may have increased venous pressures and hence facilitated a hydrostatic increase in brain water content. However, we waited a full hour after infusing drugs. During this time, there was an obvious (but unmeasured) diuresis and a MAP decrease to values less than baseline. Therefore, we do not believe that there was any sustained increase in vascular volume or venous pressures. These were also short-term experiments, and it is possible that differences might have appeared with longer observation times or with repeated doses. Our goal, however, was to mimic the usual situation in the operating room, where only single doses are given and where relatively acute effects on brain swelling are of the greatest interest. We measured hemispheric water content, rather than attempting to examine changes in

small tissue samples both adjacent to and distant from the focus of the injury. It is hence possible that regional changes in furosemide-induced water content might have been missed. However, the overall effect of drug therapy on ICP or brain bulk is likely mediated by global change in brain water, rather than regional effects. Finally, we measured only brain water content and not ICP. As noted above, both animal and human studies have shown that furosemide can reduce ICP. It is hence possible that ICP was reduced in our furosemide-treated animals. Nevertheless, even if this were the case, the change cannot be attributed to changes in brain water content.

The inconsistency between our inability to demonstrate an effect of furosemide on water content and the ability of this drug to reduce ICP remains unexplained. Other studies have also failed to demonstrate an effect of furosemide on cerebral edema, or a unique contribution of furosemide when given in combination with mannitol. Because ICP is determined by the volume of three primary intracranial tissue compartments—blood, tissue, and CSF—the potential remains that furosemide (or furosemide plus mannitol) might influence ICP by reducing either CSF or blood volume. As described above, furosemide in very large doses reduces CSF production (and possibly CSF volume). However, the lower doses of furosemide that have been shown to reduce ICP do not reduce CSF production. Almost no work has been done on the cerebrovascular effects of furosemide. The only study that examined the effect of furosemide on cerebral blood flow in normal animals was reported by Rovere and Scremin.⁴³ These authors demonstrated an *increase* in cerebral blood flow in response to topical and systemic furosemide. Although no data exist regarding cerebral blood volume, acute cerebral vasodilation is inconsistent with a reduction in ICP. It is difficult to reconcile the absence of changes in brain water content (which makes up nearly 80% of tissue volume), the lack of direct vascular effect consistent with reduction in ICP, and the apparently high doses required to reduce CSF production with a reduction in ICP.

Our results also need to be compared and contrasted with a recent publication by Mayzler *et al.*⁴⁴ that examined the impact of hypertonic saline with or without furosemide on brain water content. These authors noted that hypertonic saline (in a dose sufficient to increase plasma osmolality from roughly 298 to 325 mOsm/kg, given before impact) did not prevent the increase in water content produced by an impact injury, as measured at 2 h after injury. However, when hypertonic saline was combined with furosemide (2 mg/kg), water content was similar to that in control animals (no impact). It is, however, difficult to compare the studies directly. In the study by Mayzler *et al.*, drugs were administered before impact, animals were allowed to awaken after injury, and water content was measured

between 0.5 and 2 h after impact. By contrast, in our study, drugs were given in much larger doses (*e.g.*, the maximum mannitol dose increased osmolality to approximately 350 mOsm/kg) between 2.5 and 3 h after injury, with water content measured 1 h later. Our animals were also anesthetized and ventilated throughout the experiment. The dosage differences might be important; in the face of lesser changes in osmolality, the impact of furosemide may be apparent. This would not be consistent, because the water content values seen with 4 g/kg mannitol plus 4 mg/kg furosemide—although not directly examined statistically—do not seem different from those seen with 4 g/kg mannitol alone. Nevertheless, the discrepancies do raise the possibility that different results may occur with different osmotically active drugs (mannitol *vs.* saline) given at different times in relation to the injury.

In summary, these experiments demonstrated the expected dose-related effects of mannitol on plasma osmolality and brain water content in the injured as well as the contralateral hemisphere. However, we were unable to demonstrate any effect of furosemide, alone or in combination with mannitol.

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