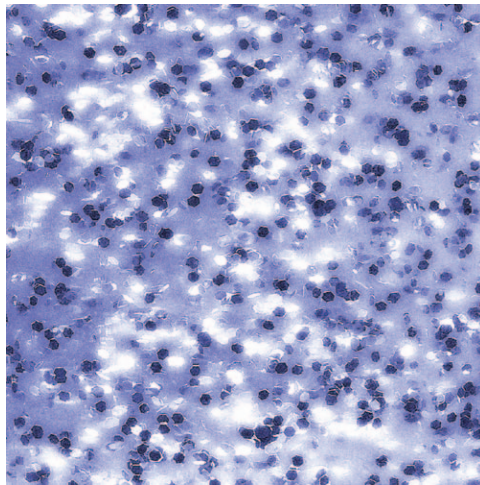


Hyperosmolar Therapy and the Brain

A Hundred Years of Hard-earned Lessons

IN 1898, Starling¹ described the forces governing fluid movement across various membranes. In 1919, Weed and McKibben showed that hypertonic fluids reduced intracranial pressure (ICP) and brain bulk,^{2,3} a finding immediately adopted clinically. Different compounds were tried (saline, glucose, sucrose, magnesium sulfate, urea, glycerol, and others), with mannitol (introduced in the 1960s) and hypertonic saline as the mainstays of therapy today. And yet, despite 114 yr of study and 93 yr of use, clinicians often seem uncertain about which agent to select, about how to use them, and, most importantly, about how they work. The article in the current issue of ANESTHESIOLOGY by Wang *et al.*⁴ is an example of the ongoing effort to resolve this uncertainty. The authors compared and contrasted the effects of mannitol and hypertonic saline, with and without added furosemide, on brain water content in normal rats. The authors gave carefully prepared, equivolume, equimolar doses of the two fluids* to normal rats and examined the time course of serum



“I have argued that, at least for single bolus use, there is little difference between mannitol and hypertonic saline.”

Photo: J. P. Rathmell.

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* The authors are to be congratulated for meticulous attention to study design. Too many studies comparing mannitol and hypertonic saline have failed to insure identical osmolar loads and fluid volumes. However, since even tiny differences in serum osmolality can result in important differences in water content, ICP *etc.*, the ideal experiment would match both the actual serum osmolalities achieved and the time needed to achieve them. Unfortunately, this is nearly impossible to do in practice.

† The values we get back from our hospital laboratory, typically measured by freezing-point depression - the same property by which salt is used to melt ice - is osmolality (mOsm/kg); the value you see on a bag of iv fluid is osmolarity (mOsm/l), a calculated number. The values are similar except in ionized solutions where attraction between charged particles reduces the effective number of truly independent particles, meaning that osmolality will be less than osmolarity.

‡ Mannitol and sodium actually do differ slightly in terms of their “reflection coefficients,” a measure of their permeability across the blood brain barrier (mannitol = 0.9, sodium = 1.0). However, this difference is almost certainly irrelevant in most clinic situations, particularly following single bolus doses.

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osmolality and brain water content. As expected, both solutions reduced water content. The initial decrease was slightly greater with mannitol than hypertonic saline probably because the resultant serum osmolality was slightly greater. Over the course of 5 h, average water content with mannitol was also lower than with hypertonic saline, again because osmolality tended to be higher. Furosemide had no effect on its own, but adding it to hypertonic saline resulted in a small increase in serum osmolality and a further reduction in brain water content.

Those are the basic findings. But, what, in fundamental terms, does this study—and others—tell us about hyperosmolar therapy? The answers are perhaps more straightforward than often recognized. Without minimizing the work of Wang *et al.*, almost every-

thing about hyperosmolar therapy can be understood by a careful study of Starling, along with basic college-level physical chemistry and physiology. The following is intended as a brief (and somewhat simplified) primer on the subject.

First, the osmolality of a solution is dependent only on the number of dissolved particles in a mass of water; a solution of 280 mOsm/kg contains 280 mmoles of independent particles per kilogram of water.† The nature of those particles does not matter; a mannitol molecule and a sodium ion are osmotically identical. Second, for osmotic forces to act, one must establish a concentration gradient across a semipermeable membrane (semipermeable defined as “water moves, solute doesn’t”). If no gradient can be established, for example, if the blood–brain barrier is disrupted, or if the “particle” can move across the membrane (*e.g.*, glucose), then water will not move (or not move as much).‡ Third, osmotic forces are powerful; increasing serum osmolality by 20 mOsm/kg (easily achieved with 1 g/kg of mannitol) is equivalent to a 380 mmHg change in driving force! Small changes in the osmotic gradient can move a LOT of water rapidly.

◆ This Editorial View accompanies the following article: Wang LC, Papangelou A, Lin C, Mirksi MA, Gottschalk A, Toung TJK: Comparison of equivolume, equiosmolar solutions of mannitol and hypertonic saline with or without furosemide on brain water content in normal rats. ANESTHESIOLOGY 2013; 118:903-13.

Fourth, the normal brain (with an intact blood–brain barrier) is an exquisitely sensitive osmometer. As osmolality increases and decreases, brain water content increases and decreases in an inverse-linear fashion. Fifth, the time course of brain water content is dependent on the pharmacokinetics of the changing osmolality (not necessarily the kinetics of the administered agent). Sixth, hyperosmolar therapy is not directly dependent on a diuresis; mannitol given to anephric animals still results in brain shrinkage. However, the loss of water *via* diuresis and the volume and nature of fluids given to replace lost volume can influence the osmolar pharmacokinetics.

There are a few wrinkles. First, as noted, the normal brain is a sensitive osmometer. The damaged brain—with an open blood–brain barrier—is not; osmotic forces act only on tissue with an intact barrier.⁵ Therefore, the reduction in ICP that we see with treatment is due to water moving out of remaining normal brain, not out of damaged tissue. Second, even the normal blood–brain barrier is not infinitely impermeable to clinically relevant osmotically active particles. Over long periods of time (hours, certainly days), these will begin to diffuse into the tissue (or they may enter *via* areas of disruption). Third, most biological tissues resist sustained reductions in volume. When exposed to a hypertonic environment, cells shrink—and almost immediately begin to respond. Initially (over minutes), various ions (*e.g.*, sodium, chloride, and potassium) enter the cell, resulting in an increase in intracellular osmolality. Over longer time periods (hours), cells begin to accumulate small molecules (organic osmolytes or “idiogenic osmoles”) that also serve to increase intracellular osmolality. These two factors will act to draw water back into the cells.⁶ Fourth, an increase in osmolality triggers the release of vasopressin, which will act to increase the reabsorption of free water by the kidneys. All of these factors can combine to produce a “rebound” increase in brain volume and ICP, particularly when extracellular osmolality begins to decrease. This may indeed be seen with long-term (days) osmotic therapy (unless added increases in serum osmolality are induced—which may be dangerous). As a result, continuous hyperosmolar therapy may be problematic. In addition, reversing long-term hyperosmolality can be hazardous—the same forces that draw water out of brain as osmolality increases will drive water back into the brain as osmolality decreases. However, these issues are probably of little or no importance when single doses of these compounds are given acutely in the operating room or intensive care unit.

So what are the differences between mannitol and hypertonic saline? There have been many studies done under many conditions—and many have not been well conducted.‡ As noted, osmotically there are no meaningful differences. Either agent, if given to achieve an identical increase in serum osmolality, will result in essentially identical initial reductions in water content and equivalent reductions in ICP and brain shrinkage.⁷ Practically speaking,

the administration of 500 ml of 20% mannitol or 500 ml of 3% saline will achieve the same goal. Both will also result in equivalent initial increases in intravascular volume (because both draw water from tissue into the intravascular space) and have the potential for inducing acute volume overload, for example, congestive heart failure in patients with compromised cardiac function. The differences lie in the resultant electrolyte changes and pharmacokinetics. Mannitol results in a marked decrease in serum sodium (as the influx of water dilutes serum electrolytes), whereas hypertonic saline increases serum sodium (although water influx will buffer the sodium increase). Because mannitol is not reabsorbed by the kidneys, hypertonic saline may have a somewhat longer duration of action. The next difference is diuresis. Mannitol results in a profound diuresis and loss of total body water that can result in hypovolemia. By contrast, hypertonic saline is not accompanied by as great a diuresis (although there is some increase in urine output simply due to volume expansion).⁷ This is nicely demonstrated in the Wang *et al.* study; rats given mannitol lost substantially more weight (and body water) over the 5-h study than did animals given hypertonic saline. These difference points to what is the biggest advantage of hypertonic saline; when given to hypovolemic or bleeding patients (*e.g.*, after major trauma), subsequent volume (and electrolyte) management be simplified. If mannitol-induced urine output (which results in losing water in excess of sodium) is replaced with the balanced salt solutions or normal saline, serum sodium may rebound to higher-than-baseline values. Serious hypernatremia can result—but of course, overly aggressive infusion of hypertonic saline can yield the same result.

What about furosemide? Furosemide—usually in doses approaching or exceeding 1 mg/kg—can reduce ICP (albeit much slower than mannitol).⁸ But, as shown by Wang *et al.* and others, it does not directly reduce brain water content.^{4,9,10} Its mechanism of action *vis a vis* ICP is unknown, but probably involves changes in cerebrospinal fluid production and volume. Then why did furosemide, when added to hypertonic saline, result in an additional reduction in brain water content? Simple. Furosemide, like mannitol, results in a water diuresis and the loss of water serves to augment the hypernatremia (and hyperosmolality) produced by hypertonic saline. Note, however, that the augmented diuresis produced by the added furosemide may now result in hypovolemia—something that we may have wished to avoid by using hypertonic saline.

The summary above is intended to help operating room–based clinicians better understand the use of these agents; I have generally avoided discussing long-term osmotherapy in a critical care setting, and I have not discussed some of the other properties of these drugs that may or may not have any clinical relevance (*e.g.*, vasoconstriction produced by hyperosmolality and hemodilution, free-radical effects). I have argued that, at least for single

bolus use, there is little difference between mannitol and hypertonic saline. Unfortunately, well done comparative trials are few¹¹; I will concede that in some settings (*e.g.*, trauma), some small differences in ICP control may exist (although again, these may be related to differing osmolalities or osmotic kinetics). But, in an era of “evidence-based medicine,” we are constantly challenged to answer the question “does it improve outcome.” We do not know—the work has not been done. But no neurosurgeon, neurologist, neurosurgical anesthesiologist, or intensivist doubts the value of these drugs. Tens of thousands of physicians have witnessed the resultant rapid decrease in ICP, the visible shrinkage of a swollen brain, the normalization of a dilated pupil, or the awakening of a comatose patient. That is probably evidence enough.

Michael M. Todd, M.D., Department of Anesthesia, University of Iowa Carver College of Medicine, Iowa City, Iowa. michael-todd@uiowa.edu

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