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Salt, water and cerebral edema

BY DESMOND BOHN, MB, BCH, FRCPC

The administration of IV fluids is probably the most commonly performed procedure in hospitalized patients. Deciding what fluid to give and how much is not generally considered to be something that requires much intellectual thought, yet every year an unknown number of patients die because of a lack of an understanding of the principles that govern fluid and electrolyte physiology. The purpose of this issue of *Critical Care Rounds* is to highlight these principles and to explain how osmolar shifts can influence fluid movement between the extracellular fluid (ECF) and intracellular fluid (ICF) compartments, resulting in death from cerebral edema.

Sixty percent of what we are is water. Two-thirds of this is distributed in the intracellular compartment (ICF), and the remaining one-third, in the extracellular fluid compartment (ECF). Sodium (Na^+) is the major cation of the ECF, and together with chloride (Cl^-), provide the major effective osmolality of that space. As Na^+ is confined to the ECF compartment, the total body Na^+ content in a 70 kg person (14 L ECF) is $140 \times 14 = 1960$ mmol. Potassium and phosphate are the major intracellular ions and the two compartments are separated by a semipermeable membrane that allows free movement of water between the ICF and the ECF with osmolar equilibrium between the two.

Serum osmolality is regulated by osmoreceptors in the hypothalamus. Any minor change in tonicity ($>2\%$) is sensed by these receptors and causes the release of anti-diuretic hormone (ADH)¹ that acts on V2 receptors in the collecting duct, opening aquaporin channels, and causing water reabsorption and the excretion of a concentrated urine. A reduction in serum osmolality normally inhibits the release of ADH and causes the excretion of dilute urine. ADH secretion is also controlled to a lesser extent by baroreceptors in the heart and great vessels, such that in the presence of ECF contraction, ADH is released, resulting in increased urine osmolality. A normal 70 kg human filters 140 L of water at the glomerulus, and the majority (70%) is reabsorbed in the proximal convoluted tubule. In the presence of ADH, a maximal urine concentration of 1200 mosmoles is possible and with inhibition of ADH, maximally dilute urine is 50 mosmoles.

The effective serum osmolality is derived from Na^+ and glucose, and any change in these molecules will result in water moving between the ECF and ICF. Urea is



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not an effective osmole because it moves freely across the cell membrane. The main clinical manifestation of the acute changes in tonicity is mediated by changes in the ICF compartment, particularly in the brain. The presence of hyponatremia usually implies an expansion of the ICF compartment except in situations of diabetic ketoacidosis (see below). Conversely, the presence of hypernatremia implies a contraction of the ICF compartment. In contrast to the ICF compartment, the state of the ECF compartment cannot be estimated by the measured osmolality. In general, there is no predictable relationship between the ECF compartment and either serum sodium concentration or urinary sodium excretion (Table 1).

Acute hyponatremia and I.V. fluid administration

Regulation of salt and water homeostasis is frequently abnormal in hospitalized patients. Hyponatremia ($\text{Na}^+ < 140 \text{ mmol/L}$) is the most common electrolyte abnormality, with an incidence of 2.5% in the general hospital population.² Except in rare circumstances (eg, hyperglycemia or hypertriglyceridemia), reduced serum sodium indicates a low-serum osmolality and an expanded ICF compartment.

Acute hyponatremia – defined as a fall in serum sodium to $< 130 \text{ mmol/L}$ within 48 hours – can result in acute cerebral edema and brain stem herniation. This phenomenon has been described in both adults and children and has frequently been associated with the administration of I.V. hypotonic fluids in the perioperative period.³⁻⁵ In an adult series reported by Arieff, on minor surgical operations in otherwise

healthy women, the average fluid administered in 48 hrs was 8.8 litres with a net positive balance of 7.5 litres.³ These patients clearly failed to mount the normal physiological response to the expansion of the ECF compartment, which is to produce dilute urine by the inhibition of ADH secretion. ADH secretion is stimulated by a variety of things that happen in hospitalized patients, including pain, anxiety, the use of narcotics and anaesthetic agents, surgery, and positive pressure ventilation. Similar catastrophic events have been reported in children undergoing minor surgery, as well as in non-surgical patients receiving hypotonic fluids.⁴⁻⁶

The use of these solutions is standard in pediatric practice and is based on assumptions extrapolated from studies of water requirements and energy expenditure done on *normal* children almost 50 years ago.⁷ The formulae developed from these studies are used for calculating what are commonly referred to as *maintenance* fluids, and results in the administration of large amounts of electrolyte-free water (EFW), which then requires the patient to inhibit ADH secretion in order to produce a dilute urine. Failure to do so, for the reasons outlined previously, will result in a fall in serum Na^+ , with occasional catastrophic results. The flaw in the reasoning behind the application of these formulae for fluid administration is that hospitalized patients do not necessarily follow rules that govern normal physiology. Different rules apply to sick people. The assumption should be that when Na^+ is less than 140 mmol/L – in the absence of a source of Na^+ loss – that ADH is acting. These patients should not be given hypotonic fluids, regardless of their age group.

Table 1: Lack of relation between plasma sodium concentration and volume

Osmotic and volume effects of addition of NaCl, water, and isotonic saline. Each of the interventions increased the extracellular volume and therefore urine sodium excretion, even though the plasma sodium was increased, decreased, and unchanged, respectively. Thus, there is no predictable relationship between the plasma sodium concentration and volume. When occurring acutely, the decrease in intracellular volume with hypernatremia and increase in intracellular volume with hyponatremia occurring in the brain are primarily responsible for the symptoms associated with these disturbances.

Substance added	Plasma osmolality	Plasma volume	Extracellular volume	Intracellular sodium	Urine sodium
NaCl	Increased	Increased	Increased	Decreased	Increased
Water	Decreased	Decreased	Increased	Increased	Increased
Isotonic NaCl	No change	No change	Increased	No change	Increased

Adapted from: Zaetta JM, Mohler ER, Baum R. Indications for percutaneous interventional procedures in the patient with claudication. In: *UpToDate*, Rose, BD (Ed); *UpToDate*, Wellesley, MA, 2001.

A study of over 100 children admitted to hospital with the usual spectrum of acute medical illnesses showed elevated ADH levels and low Na^+ levels (136 mmol/L) at the time of admission, compared to a cohort of elective surgical admissions who had normal Na^+ and ADH levels.⁸ Other groups particularly at risk for the development of acute hyponatremia, include elderly females treated with thiazide diuretics for hypertension who undergo hip replacement surgery,^{9,10} and patients undergoing colonoscopy.¹¹ The ingestion of the recreational drug MDMA (Ecstasy) is associated with increased secretion of ADH¹² and MDMA toxicity can present as acute hyponatremia with cerebral edema and a fatal outcome.¹³⁻²¹

At present, the standard of care in many institutions is to use only isotonic fluids containing no EFW during surgery and in the post-operative period. This will reduce the risk of a fall in serum sodium, but will not eliminate it. In a study where only Ringers lactate was used during elective surgery and through the first postoperative day, the Na^+ fell from 140 to 136 mmol/L.²² This was associated with a total I.V. intake of 5 L and a positive fluid balance of 3 L. The explanation for the fall was demonstrated when urine Na^+ was measured. Most of the patients were producing a hypertonic urine ($\text{Na}^+ > 150$ mmol/L) and they were in fact “desalinating.” The hypothesis proposed to explain this phenomenon is that large amounts of fluid are infused during surgery to restore blood pressure, which falls secondary to the vasodilatory effect of anaesthetic agents. When vasomotor tone is restored to normal at the end of the procedure, the ECF space is over-filled and the kidney responds by eliminating Na^+ .²³ Hypotonic fluids should not be used in patients from any age group unless there is a need for EFW (ie, plasma $\text{Na}^+ > 145$ mmol/L). Patients with Na^+ levels < 140 mol/L should receive isotonic fluid.

Diabetic ketoacidosis and cerebral edema

Diabetic ketoacidosis (DKA) is associated with major osmolar shifts as water moves from the ICF to the ECF compartment because of the osmolar gradient associated with the hyperglycemia. The measured plasma Na^+ frequently does not reflect the true degree of ECF contraction. The risk of developing

cerebral edema during fluid resuscitation in these patients is very real, particularly in children, and is the leading cause of death from DKA in this age group. A recently published epidemiological survey in the United Kingdom analyzed almost 3000 episodes of DKA in children over a 3-year period and found 34 cases of cerebral edema (incidence 6.8/1000) with 24% mortality and 35% morbidity.²⁴

Published series of brain imaging in children with DKA suggest that there is evidence of increased intracranial pressure (ICP) even at the time of presentation.^{25,26} There are also occasional reports of cerebral edema with fatal outcome occurring in adults.²⁷⁻³⁰ Although no one single cause can be identified, it is highly probable that rapid changes in serum osmolality will increase the risk. One of the principal causes may be rapid reductions of effective osmolality of the ECF, due to either a fall in blood glucose or serum sodium, or both, associated with the rapid administration of I.V. fluid and bolus dose insulin. Insulin administration is also known to turn on the sodium/hydrogen ion exchanger, increasing the ICF Na^+ concentration.³¹ This increase results in a rapid shift of fluid back into the ICF compartment and has been shown to result in cerebral edema in an animal model of DKA. The edema was worse when hypotonic fluids were used, as compared to isotonic fluids.³²

Although there is no consensus for the role of fluid resuscitation in cerebral edema in retrospective reviews published in the pediatric literature,³³⁻⁴¹ most would agree that large amounts of hypotonic fluids are not appropriate. In the absence of a single unifying hypothesis as to the cause of cerebral edema in DKA, a more conservative approach to fluid resuscitation would seem prudent. The greatest mortality and morbidity risk in these patients is brain swelling and not shock with cardiovascular collapse. The objective should be a gradual reduction in serum osmolality achieved with conservative fluid resuscitation and the avoidance of bolus insulin or the rapid expansion of the ECF with high volumes of hypotonic fluids.

One randomized trial in adults with DKA compared two fluid regimes.⁴² The first regime used isotonic saline at a rate of 1 L/hr for the first 4 hours, followed by 500 ml/hr for the next 4 h. The second

used 500 ml/h for the first 4 hrs, followed by 250 ml/hr for the next 4 hrs. The patients managed with the more conservative fluid regime corrected their acidosis in a shorter period of time.

Acute hyponatremia and cerebral salt wasting

Acute hyponatremia is also known to be associated with subarachnoid hemorrhage and traumatic brain injury. The diagnosis is usually made in patients who have had a fall in plasma Na⁺ associated with a hypernatric urine. For some years this was considered to be due to SIADH (syndrome of inappropriate secretion of antidiuretic hormone), but more recently, the concept of cerebral salt wasting (CSW), first described in the 1950s,^{43,44} is the more favoured explanation in the neurosurgical literature.⁴⁵⁻⁴⁹ The postulated mechanism is the release of natriuretic peptides causing a salt and water diuresis, and the increased levels of brain natriuretic peptide (BNP) that have been demonstrated in patients with subarachnoid hemorrhage (SAH).⁵⁰

It is important to make the distinction between the diagnosis of SIADH and CSW. In SIADH, patients are euvolemic or hypervolemic and should be treated with fluid restriction. In CSW, patients waste water and salt and are hypovolemic, requiring water and salt replacement therapy in order to reduce the possibility of cerebral infarction.⁵¹ However, to make a sustainable diagnosis requires more than the demonstration of high urinary sodium excretion, which can also be seen in SIADH. A negative balance for *both* water and salt needs to be present to confirm a diagnosis of CSW.⁵² This information is frequently lacking in published case reports or case series. More careful scrutiny of tonicity balance data, taking into account all administered fluid, shows that these patients are frequently not in negative salt and water balance when the diagnosis is suspected.⁵³ The question then arises about whether the diuresis and natriuresis is due to therapy, particularly the use of triple H therapy (hemodilution, hypervolemia,

hypertension) to prevent vasospasm in SAH (hypertension, hypoviscosity). The very high amount of saline administered, combined with driving up the systemic arterial pressure with vasopressors, frequently results in the kidney producing a large amount of both water and salt.

An alternative hypothesis exists for the hyponatremia seen in association with traumatic brain injury and SAH. These CNS lesions are associated with increased adrenergic output, leading to a stimulus for increased salt and water excretion by the kidneys. This stimulus is frequently compounded by the administration of large amounts of saline and the use of vasopressors. Although speculative, it is interesting to note that increasing reports of CSW in the neurosurgical literature seem to coincide with the introduction of triple H therapy, which begs the question: "Is it the disease or is it the doctor?"

Summary

The administration of I.V. fluid therapy in hospitalized patients should be based on an understanding of the importance of avoiding osmolar shifts. Patients with a serum sodium of <138 mmol/L should be assumed to have release of ADH and an expanded ICF compartment, in the absence of an alternative explanation. These patients should receive only isotonic fluids, while hypotonic solutions should be reserved for those with a true EFW deficit.

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Abstracts of Interest

Risk factors for cerebral edema in children with diabetic ketoacidosis.

GLASER N, BARNETT P, McCASLIN I, ET AL, THE PEDIATRIC EMERGENCY MEDICINE COLLABORATIVE RESEARCH COMMITTEE OF THE AMERICAN ACADEMY OF PEDIATRICS. DAVIS, CALIFORNIA

BACKGROUND: Cerebral edema is an uncommon but devastating complication of diabetic ketoacidosis in children. Risk factors for this complication have not been clearly defined.

METHODS: In this multicenter study, we identified 61 children who had been hospitalized for diabetic ketoacidosis within a 15-year period and in whom cerebral edema had developed. Two additional groups of children with diabetic ketoacidosis but without cerebral edema were also identified: 181 randomly selected children and 174 children matched to those in the cerebral-edema group with respect to age at presentation, onset of diabetes (established vs. newly diagnosed disease), initial serum glucose concentration, and initial venous pH. Using logistic regression we compared the three groups with respect to demographic characteristics and biochemical variables at presentation and compared the matched groups with respect to therapeutic interventions and changes in biochemical values during treatment.

RESULTS: A comparison of the children in the cerebral-edema group with those in the random control group showed that cerebral edema was significantly associated with lower initial partial pressures of arterial carbon dioxide (relative risk of cerebral edema for each decrease of 7.8 mm Hg [representing 1 SD], 3.4; 95 percent confidence interval, 1.9 to 6.3; $P < 0.001$) and higher initial serum urea nitrogen concentrations (relative risk of cerebral edema for each increase of 9 mg per deciliter [3.2 mmol per liter] [representing 1 SD], 1.7; 95 percent confidence interval, 1.2 to 2.5; $P = 0.003$). A comparison of the children with cerebral edema with those in the matched control group also showed that cerebral edema was associated with lower partial pressures of arterial carbon dioxide and higher serum urea nitrogen concentrations. Of the therapeutic variables, only treatment with bicarbonate was associated with cerebral edema, after adjustment for other covariates (relative risk, 4.2; 95 percent confidence interval, 1.5 to 12.1; $P = 0.008$).

CONCLUSIONS: Children with diabetic ketoacidosis who have low partial pressures of arterial carbon dioxide and high serum urea nitrogen concentrations at presentation and who are treated with bicarbonate are at increased risk for cerebral edema. *N Engl J Med* 2001;344(4):264-269.

Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination.

STEELE A, GOWRISHANKAR M, ABRAHAMSON S, MAZER CD, FELDMAN RD, HALPERIN ML. TORONTO, ONTARIO.

BACKGROUND: To show that hyponatremia would occur in patients 24 hours after surgery if only near-isotonic solutions are given and to evaluate the mechanisms responsible for hyponatremia in this setting.

DESIGN: Prospective cohort study.

SETTING: University medical center.

PATIENTS: 22 women who were having uncomplicated gynecologic surgery with infusion of near-isotonic solutions only (sodium

chloride, 154 mmol/L, or Ringer lactate [sodium, 130 mmol/L, and potassium, 4 mmol/L]).

MEASUREMENTS: Plasma electrolyte levels were measured at the time of induction of anesthesia and 24 hours later. Data on the balance of water and electrolytes were obtained for the same 24-hour period.

RESULTS: At the time of induction of anesthesia, the plasma sodium concentration was 140 ± 1 mmol/L; 24 hours later, it decreased in 21 of 22 patients (mean decrease, 4.2 ± 0.4 mmol/L [$P < 0.001$]; lowest level, 131 mmol/L in 2 patients). The urine remained hypertonic (peak sodium plus potassium concentration in urine, 294 ± 9 mmol/L) in all patients for the first 16 hours after induction of anesthesia.

CONCLUSIONS: Postoperative hyponatremia occurred within 24 hours of induction of anesthesia when only near-isotonic fluids were infused. Hyponatremia was generally caused by generation of electrolyte-free water during excretion of hypertonic urine—a desalination process. This electrolyte-free water was retained in the body because of the actions of antidiuretic hormone. If the pathophysiology of this hyponatremic state is understood, recommendations for its prevention and treatment can be deduced.

Ann Intern Med 1997;126(12):1005-1006.

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