REVIEW ARTICLE

DISORDERS OF FLUIDS AND ELECTROLYTES

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Disorders of Plasma Sodium — Causes, Consequences, and Correction

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HUMAN CELLS DWELL IN SALT WATER. THEIR WELL-BEING DEPENDS ON the ability of the body to regulate the salinity of extracellular fluids. By controlling water intake and excretion, the osmoregulatory system normally prevents the plasma sodium concentration from straying outside its normal range (135 to 142 mmol per liter). Failure of the system to regulate within this range exposes cells to hypotonic or hypertonic stress. This review considers the causes and consequences of an abnormal plasma sodium concentration and offers a framework for correcting it.

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N Engl J Med 2015;372:55-65.
DOI: 10.1056/NEJMra1404489

PLASMA SODIUM CONCENTRATION AND EXTRACELLULAR TONICITY

The plasma sodium concentration affects cell volume. The term "tonicity" describes the effect of plasma on cells — hypotonicity makes cells swell and hypertonicity makes them shrink. Hypernatremia always indicates hypertonicity. Hyponatremia usually indicates hypotonicity, but there are exceptions (e.g., hyperglycemic hyponatremia and pseudohyponatremia) that are not covered in this review.

PLASMA SODIUM CONCENTRATION AND THE ELECTROLYTE AND WATER CONTENT OF THE BODY

Solute concentrations (osmolalities) must be equal inside and outside of cells because water channels (aquaporins) make cell membranes permeable to water.[1,2] The "sodium pump" (Na^+/K^+–ATPase) functionally excludes sodium from cells, exchanging it for potassium by means of active transport. Although sodium is largely extracellular and potassium is intracellular, body fluids can be considered as being in a single "tub" containing sodium, potassium, and water, because osmotic gradients are quickly abolished by water movement across cell membranes. As such, the concentration of sodium in plasma water should equal the concentration of sodium plus potassium in total body water. This theoretical relationship was validated empirically by Edelman et al.,[3] who used isotopes to measure exchangeable body cations and water.

Edelman and colleagues described the relation between these variables with the following equation:

$$[Na^+] \text{ in plasma } H_2O = 1.11 \times \frac{(Na^+_e + K^+_e)}{\text{total body } H_2O} - 25.6,$$

where Na^+_e is exchangeable sodium, K^+_e exchangeable potassium, and H_20 water. This equation has an intercept (–25.6); the regression line relating plasma sodium

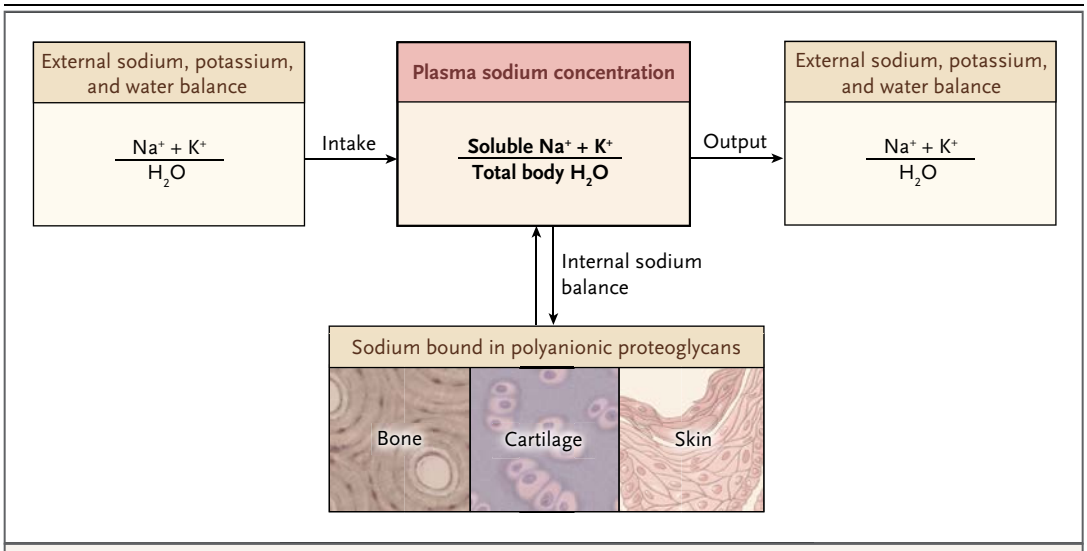

Figure 1. Internal and External Solute and Water Balance and the Plasma Sodium Concentration.

The plasma sodium concentration is determined according to the ratio of the content of sodium and potassium in the body (the numerator of the ratio) to total body water (the denominator of the ratio). This concentration is altered by net external balances (intake minus output) of sodium, potassium, and water and by internal exchange between sodium that is free in solution and sodium that is bound to polyanionic proteoglycans in bone, cartilage, and skin.

to the ratio of exchangeable ($Na^+ + K^+$) to total body water does not pass through zero because not all exchangeable sodium is free in solution.[4] A substantial amount of sodium is bound to large polyanionic macromolecules called proteoglycans, which make up the ground substance of bone, connective tissue, and cartilage (Fig. 1).[1] The sodium concentration of cartilage is nearly twice that of plasma. The osmotic force created by the high sodium concentration (about 40 mm Hg for every difference in concentration of 1 mmol per liter) maintains the high water content in the tissue, allowing it to withstand pressures that can exceed 20,000 mm Hg during exercise.[5]

When it became known that much of the sodium in the body is bound to bone, cartilage, and connective tissue, it was hypothesized that these tissues could serve as sodium reservoirs, taking up or releasing sodium in response to the needs of the body.[6] Despite early evidence supporting the concept of a sodium reservoir,[7-9] this theory lost favor[10] and was not pursued for half a century. However, the past decade has seen renewed interest in stored sodium.[11] In patients who consume high-salt diets, sodium can accumulate in the body, seemingly disappearing without a change in the plasma sodium concentration, body weight, or extracellular fluid volume.[12] Sodium, potassium, and water balance do not always account for changes in the plasma sodium concentration during recovery from hyponatremia.[13] Proteoglycans in skin serve as a sodium reservoir, and the number of negative charges available to bind sodium varies in response to the sodium concentration of interstitial tissue.[14-16] In experiments in rats, chronic hyponatremia has been shown to be a more potent cause of osteopenia than vitamin D deficiency, and loss of sodium from bone exceeded the loss of calcium from bone. The activity of osteoclasts is increased in chronic hyponatremia owing to a direct effect of sodium and possibly vasopressin on these cells.[17]

In humans, chronic hyponatremia is associated with osteoporosis and fractures. During extreme-endurance athletic events lasting several hours, bone density decreases measurably, and the decrease in bone density correlates remarkably closely with changes in the plasma sodium concentration.[17,18]

PLASMA SODIUM CONCENTRATION AND TONICITY BALANCE

A simplified version[19] of the equation reported by Edelman et al. is

$$\text{plasma } [Na^+] = \frac{\text{total body } (Na^+ + K^+)}{\text{total body } H_2O}.$$

The plasma sodium concentration is altered by changes in overall sodium and potassium balance (the numerator of the simplified equation) and water balance (the denominator) (Fig. 1). To understand or roughly predict changes in the plasma sodium concentration, the overall tonicity of the diet and intravenous fluids and the overall tonicity of gastrointestinal fluids, sweat, and urine must be considered. Like the plasma sodium concentration, which is determined by the concentrations of sodium and potassium in body water, the tonicity of these fluids is defined by their concentrations of sodium plus potassium.

It is not possible to predict the effect of administering intravenous fluids on the plasma sodium concentration without considering concurrent urinary losses. The electrolyte concentration (sodium plus potassium) of urine, and not its osmolality (which includes electrolytes, urea, and glucose), determines the effect of urine on the plasma sodium concentration. Urine is hypotonic if its electrolyte concentration is lower than that of plasma; because it is partly composed of electrolyte-free water, excretion of hypotonic urine will increase the plasma sodium concentration. Conversely, urine is hypertonic if its electrolyte concentration is higher than that of plasma; excretion of hypertonic urine will lower plasma sodium concentrations.[20]

Isosmolar or hyperosmolar urine containing mostly urea (an end product of protein metabolism) may be nearly electrolyte-free.[20,21] Excretion of urea owing to recovery from azotemia, catabolism, or a high-protein diet will cause hypernatremia unless there is replacement of the free water that has been lost.[22] Because it increases excretion of electrolyte-free water, urea has been used to treat hyponatremia.[23,24]

SODIUM AND THE BLOOD–BRAIN BARRIER

Sodium readily crosses systemic capillary membranes through clefts between endothelial cells.[25] Consequently, in most tissues, the sodium concentrations of plasma and interstitial fluid are nearly identical, with a small difference created by intravascular albumin.[1,25] In contrast, brain capillaries have tight endothelial junctions and are lined by astrocytic foot processes, creating a blood–brain barrier that sodium cannot cross (Fig. 2).[26] Consequently, an abnormal plasma sodium concentration causes water to enter or leave brain tissue. Because of the confines of the skull, only a small degree of brain swelling or shrinkage is compatible with life.

REGULATION OF THE PLASMA SODIUM CONCENTRATION

Since the plasma sodium concentration affects brain volume, it is not surprising that the cell-volume receptors that are responsible for adjusting thirst and vasopressin secretion are located in the brain. Osmoreceptors, which are more accurately called tonicity receptors, are hypothalamic neurons that express transient receptor potential cation channel subfamily vanilloid member 1 (TRPV1) and member 4 (TRPV4) channels on their cell membranes.[27,28]

Transient receptor potential cation channels belong to a large family of molecules. They were first identified as photoreceptors in fruit flies and were later discovered to serve as receptors for a variety of sensations throughout nature.[29] For example, transient receptor potential V (or vanilloid) (TRPV) channels respond to capsaicin, a vanilloid that causes the burning sensation associated with the ingestion of chili peppers. TRPV1, which is a member of the TRPV family of receptors, was identified in mutant *Caenorhabditis elegans* roundworms that did not avoid hyperosmotic environments. Insertion of a mammalian *TRPV4* gene into the genome of mutant *C. elegans* roundworms restored normal worm behavior. The *TRPV1* gene is required for normal functioning of isolated osmoreceptor neurons, and genetically engineered mice that lack genes for TRPV1 and TRPV4 have abnormal osmoregulation. Polymorphisms in genes encoding the TRPV4 channel have been identified in humans. Healthy aging men who are positive for the $TRPV4^{P19S}$ polymorphism are more likely to have mild hyponatremia than are men without this polymorphism.[30]

In normal osmoregulation, both thirst and vasopressin secretion are inhibited when the plasma sodium concentration is decreased below 135 mmol

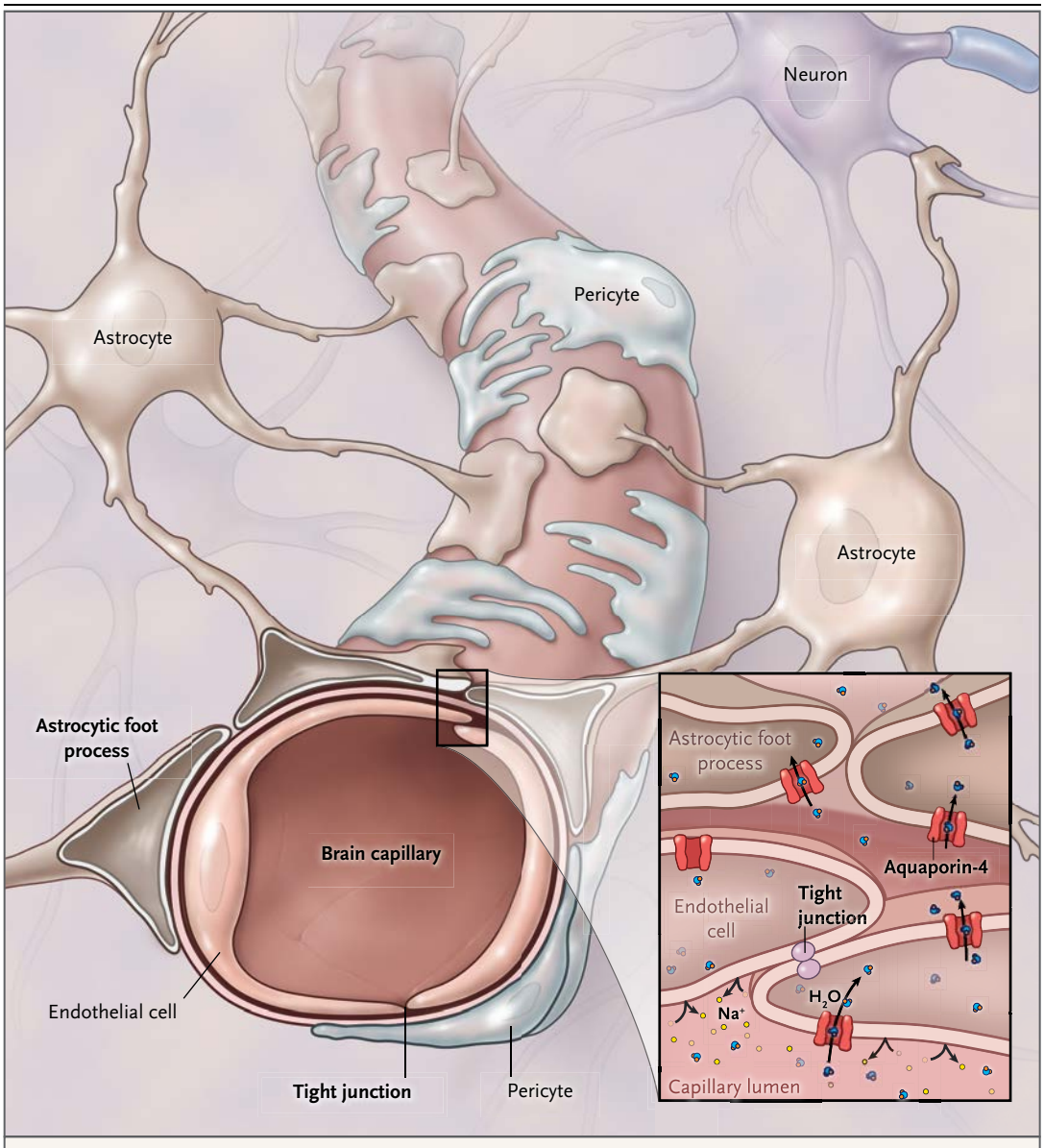

Figure 2. Astrocytes and the Neurovascular Unit.

Brain capillaries have tight junctions and are lined by astrocytic foot processes expressing aquaporin-4 water channels that make them permeable to water but not to sodium. Astrocytes, which are spatially and functionally related to endothelial cells, neurons, pericytes, and microglia, provide the brain with its first line of defense against the osmotic stress caused by sodium disorders.

per liter. In the absence of vasopressin, urine osmolality decreases to as low as 50 mOsm per kilogram. In persons who consume a typical Western diet, with an output of urinary solute of about 900 mOsm daily, a urinary solute concentration of 50 mOsm per liter yields 18 liters of urine (750 ml per hour).[20]

Although individual responses vary,[31] vasopressin is usually detectable at a plasma sodium concentration above 135 mmol per liter, and levels of vasopressin increase linearly with increasing sodium levels.[32] The hormone may also be secreted in response to circulatory inadequacy,[33] or it may be secreted "inappropriately," and sometimes ectopically, with no osmotic or hemodynamic stimulus.[34] (Vasopressin secretion

without an osmotic or hemodynamic abnormality to account for it is termed "inappropriate."[34]) Once secreted, vasopressin binds to its V2 receptor on basolateral membranes of principal cells lining the renal collecting duct.[27] In the presence of vasopressin, aquaporins are inserted into the luminal membrane, allowing water to flow out, attracted by the high solute concentration of the surrounding medullary interstitium. When the plasma sodium level increases to approximately 145 mmol per liter, vasopressin levels are normally high enough to result in maximally concentrated urine (about 1200 mOsm per kilogram). The presence of a dilute urine when the plasma sodium concentration is above 145 mmol per liter implies either deficient vasopressin secretion (as in neurogenic diabetes insipidus) or failure of the kidneys to respond to vasopressin (as in nephrogenic diabetes insipidus) (see Case 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[27]

However, even complete diabetes insipidus (with total absence of vasopressin or no tubular response to vasopressin) generally does not cause hypernatremia, because thirst prompts replacement of urinary losses of water.[28] Hypernatremia develops if water is unavailable, if the urge to drink is impaired (hypodipsia), or if patients are too young, old, or sick to seek water themselves.[35]

Maximal dilution of urine prevents hyponatremia unless water intake is extraordinarily large (>1 liter per hour) (e.g., in patients with schizophrenia who drink water compulsively)[36] or the rate of urinary solute excretion is extremely low (e.g., in beer drinkers who eat very little).[20,37] Except in these scenarios, hypotonic hyponatremia is associated with an impaired ability of the body to dilute urine because of diminished sodium transport in renal-diluting sites (most commonly because of the use of diuretics),[38] the presence of vasopressin,[39,40] or, rarely, an inherited activating mutation of the vasopressin receptor.[41] Because vasopressin, along with renin, angiotensin, aldosterone, and the sympathetic nervous system, participates in the neurohumoral response to inadequate circulation,[33] vasopressin-mediated hyponatremia may complicate hypovolemia or states that lead to edema (e.g., heart failure and cirrhosis).[40]

Many causes of hyponatremia (e.g., hypovolemia, medications, cortisol deficiency, nausea, pain, or stress) are reversible — either by treatment or the passage of time.[39] Once the cause of hyponatremia resolves, the normal osmoreceptor response to a low plasma sodium concentration inhibits vasopressin secretion, resulting in excretion of maximally dilute urine and resolution of hyponatremia.[42,43]

Administration of a vasopressin antagonist will also result in the excretion of dilute urine (also known as a "water diuresis" or "aquaresis") despite the continued presence of vasopressin. Therefore, vasopressin antagonists increase the plasma sodium concentration and are approved by the Food and Drug Administration for the treatment of hyponatremia caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or by heart failure.[44]

URINARY SODIUM AND THE PLASMA SODIUM CONCENTRATION

Urinary excretion of sodium is relatively independent of plasma sodium levels; measurement of urinary sodium levels can help to distinguish between SIADH and hypovolemic hyponatremia.[34,45,46] Excretion of sodium responds to intravascular volume, increasing with volume expansion and decreasing with volume depletion. Water retention due to SIADH expands extracellular fluid volume, resulting in increased urinary excretion of sodium despite hyponatremia.[47]

Excretion of sodium in SIADH restores normal extracellular volume, but hypertonic urinary losses also exacerbate hyponatremia.[48] For this reason, SIADH should not be treated with isotonic solutions such as 0.9% saline or Ringer's lactate, because infused sodium will be excreted in smaller volumes of urine, leading to net retention of electrolyte-free water. Such a sequence is common in patients with subarachnoid hemorrhage; saline is prescribed to maintain cerebral perfusion, but vasopressin released by neurologic injury concentrates the urine (see Case 2 in the Supplementary Appendix).[49,50]

CAUSES OF RAPID CHANGES IN THE PLASMA SODIUM CONCENTRATION

The plasma sodium concentration will decrease rapidly if the amount of water ingested or infused exceeds the capacity of the kidneys to excrete free water. The plasma sodium concentration increas-

es rapidly if large amounts of concentrated salt are ingested or infused or if there are large, unreplaced losses of electrolyte-free water because of aquaresis or osmotic diuresis (most commonly due to glycosuria). Loss or gain of approximately 3 ml of water per kilogram of body weight will change the plasma sodium concentration by approximately 1 mmol per liter.[51] Maximally dilute urine, whether resulting from untreated diabetes insipidus, spontaneous recovery from hyponatremia, or administration of a vasopressin antagonist, will increase the plasma sodium concentration by about 2.5 mmol per liter per hour. In the absence of urinary loss of water, 1 ml of 3% saline per kilogram of body weight will increase the plasma sodium concentration by about 1 mmol per liter.[51] Therefore, in a woman with a body weight of 50 kg, the increase in the plasma sodium level caused by a maximum water diuresis is similar to the increase caused by infusion of approximately 125 ml of 3% saline per hour.

CONSEQUENCES OF AN ABNORMAL PLASMA SODIUM CONCENTRATION

Extreme hypotonicity ruptures cell membranes; extreme hypertonicity damages the cytoskeleton and causes breaks in DNA, ultimately leading to apoptosis.[52] Given time, cells protect their volume and their survival by adjusting intracellular solute contents.[53]

Organic osmolytes are small intracellular molecules (e.g., glutamate, taurine, and myo-inositol) that are found throughout nature; their concentrations can vary without perturbing cell functions.[54] Hypotonicity promotes the release of osmolytes from cells through volume-sensitive leak pathways, while, concurrently, osmolyte-accumulating transporters (e.g., the taurine transporter TauT and the myo-inositol transporter SMIT) are down-regulated. With hypertonicity, TauT and SMIT are up-regulated.[53,54] These adaptations allow cells to maintain intracellular solute concentrations that are equal to the osmolality of hypotonic or hypertonic plasma, with little change in cell volume.[53,54]

Although osmotic disturbances affect all cells, clinical manifestations of hyponatremia and hypernatremia are primarily neurologic, and rapid changes in plasma sodium concentrations in either direction can cause severe, permanent, and sometimes lethal brain injury (Tables 1 and 2 and Fig. 3).[39,40] If severe hypernatremia develops over a period of minutes (e.g., after massive ingestion of salt that may occur in a suicide attempt), vascular injury created by a suddenly shrinking brain causes intracranial hemorrhage. Brain swelling from an abrupt onset of hyponatremia results in increased intracranial pressure, impairing cerebral blood flow and sometimes causing herniation (Fig. 3). Adaptive changes in brain osmolytes permit survival, but they may also contribute to symptoms.[55] For example, in acute hyponatremia, adaptive release of glutamate, an excitatory neurotransmitter, may increase the susceptibility to seizures; depletion of the transmitter from nerve terminals may account for some of the neurologic symptoms of chronic hyponatremia.[55]

The foot processes of astrocytes, which encircle both brain capillaries and neurons, express aquaporins (such as aquaporin-4) that allow water to cross the blood–brain barrier.[2] Astrocytes protect neurons from osmotic stress; in response to hypotonicity, a cell-to-cell transfer of taurine to adjacent astrocytes allows neurons to maintain their volume while astrocytes swell.[56] Within 24 to 48 hours after this transfer, astrocytes restore their volume through loss of organic osmolytes, but this makes them vulnerable to injury from rapid normalization of the plasma sodium concentration. Because of the down-regulation of transporters, recovery of lost brain osmolytes may take a week or longer.[55,56] Therefore, rapid correction of hyponatremia is a hypertonic stress to astrocytes that are depleted of osmolytes, triggering apoptosis, disruption of the blood–brain barrier, and, eventually, brain demyelination[57] (see the Supplementary Appendix). In experiments in animals, brain demyelination has been prevented by repletion of myo-inositol,[58] by lowering the plasma sodium concentration again promptly (within 12 to 24 hours after rapid correction of hyponatremia),[59] or by administration of minocycline (which prevents proliferation of glial cells).[60]

Brain injury after rapid correction of chronic hyponatremia manifests as a biphasic illness called the osmotic demyelination syndrome: an initial reduction in symptoms is followed by a gradual onset of new neurologic findings (see Case 3 in the Supplementary Appendix).[61] The clinical spectrum of the osmotic demyelination syndrome is broad and can include seizures, behavioral abnormalities, and movement disorders.[62] The most se-

Table 1. Treatment and Limits of Correction of Severe Hyponatremia.*

Duration	Related Behavior or Condition	Clinical Features	Initial Therapeutic Goal	Limit of Correction and Management of Overcorrection
Several hours	Self-induced water intoxication associated with psychosis, running in marathons, use of 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy")	Headache, delirium, vomiting, seizures, coma, neurogenic pulmonary edema, brain swelling with risk of fatal herniation	100-ml bolus of 3% saline three times as needed for severe symptoms; increase plasma sodium concentration by 4–6 mmol/liter in first 6 hr	Excessive correction not known to be harmful
1–2 days	Postoperative hyponatremia, especially in women and children; hyponatremia associated with intracranial disease	Headache, delirium, vomiting, seizures, coma, neurogenic pulmonary edema, brain swelling with risk of fatal herniation	100-ml bolus of 3% saline three times as needed for severe symptoms; increase plasma sodium concentration by 4–6 mmol/liter in first 6 hr	Avoid increasing plasma sodium concentration by >10 mmol/liter/day
Unknown or ≥2 days	Conditions associated with high risk of the osmotic demyelination syndrome (plasma sodium concentration, 105 mmol/liter or less; hypokalemia, alcoholism, malnutrition, liver disease)†	Malaise, fatigue, confusion, cramps, falls, 10% incidence of seizures with plasma sodium concentration <110 mmol/liter, minimal brain swelling, and no risk of herniation	Extra caution indicated for conditions associated with high risk of osmotic demyelination syndrome; 100- ml bolus of 3% saline if needed for seizures; increase plasma sodium concentration by 4–6 mmol/liter in first 24 hr	Avoid increasing plasma sodium concentration by >8 mmol/liter/day; consider lowering again if limit is exceeded, especially in patients with high risk of the osmotic demyelination syndrome

* Severe hyponatremia is defined as a plasma sodium concentration below 120 mmol per liter. In the absence of urinary loss of water, 1 ml of 3% saline per kilogram of body weight will increase the plasma sodium concentration by approximately 1 mmol per liter.

† The osmotic demyelination syndrome may develop when the plasma sodium concentration is increased rapidly in outpatients who became hyponatremic while drinking normal amounts of water and in hospitalized patients who became hyponatremic over 2 or more days.

verely affected patients become "locked in," unable to move, speak, or swallow because of demyelination of the central pons. Although osmotic demyelination may cause permanent disability or death, many patients — even those who require ventilator support — have a full functional recovery.[63] Acute hypernatremia may also cause brain demyelination, without the biphasic clinical course of the osmotic demyelination syndrome (Fig. 3).[64,65]

Chronic hypernatremia, like chronic hyponatremia, causes a reversible encephalopathy. Particularly in infants, organic osmolytes gained in the adaptation to chronic hypernatremia are lost slowly. Therefore, rehydration resulting in rapid correction of chronic hypernatremia causes seizures and a bulging fontanelle indicating cerebral edema (Fig. 3).[35,66,67]

A plasma sodium concentration that is even slightly outside the normal range increases the risk of death,[68] but few deaths associated with abnormalities in the plasma sodium concentration are related to neurologic complications.[69] The underlying disorders that produce an abnormal plasma sodium concentration may be responsible for excess mortality, but there may also be non-neurologic adverse consequences of prolonged osmotic disturbances, and observational studies have shown decreased mortality among hospitalized patients in whom the plasma sodium concentration was corrected.[70] Taurine and myoinositol, organic osmolytes that are lost from many cells in the adaptation to hyponatremia, are normally protective against oxidative injury.[54] An experimental model of chronic SIADH in rats showed that prolonged hyponatremia resulted in hypogonadism, loss of body fat, skeletal-muscle sarcopenia, and cardiomyopathy.[71]

CORRECTION OF AN ABNORMAL PLASMA SODIUM CONCENTRATION

Clinicians who treat patients with hyponatremia and hypernatremia should respond promptly to the immediate dangers posed by an acute disturbance, while being mindful of adaptations that make excessive correction potentially harmful. Aggressive interventions are indicated when the plasma sodium concentration has decreased or increased rapidly or when an abnormal plasma sodium concentration is causing severe symptoms. Therapy should be guided by frequent monitoring of the plasma sodium concentration and not by formulas alone.[43]

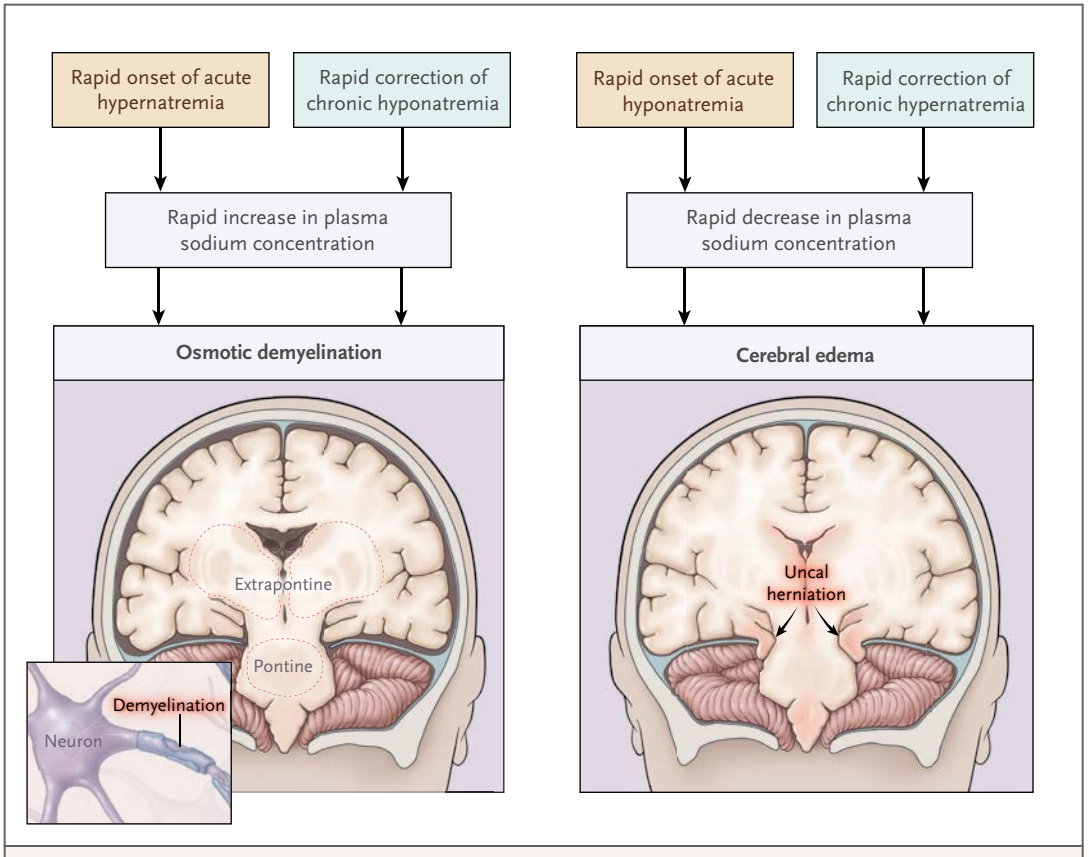

Figure 3. Consequences of Rapid Changes in the Plasma Sodium Concentration.

Both a rapid onset and a rapid correction of hyponatremia and hypernatremia can cause brain damage. A rapid increase in the level of plasma sodium, either from acute hypernatremia or from rapid correction of chronic hyponatremia, can cause osmotic demyelination. Cerebral edema is a complication of acute hyponatremia and of rapid correction of chronic hypernatremia in children.

Fatal brain swelling — a rare complication of hyponatremia that clinicians are most concerned about — has only been reported in hyponatremic patients with intracranial disease and in a few specific conditions that cause the plasma sodium concentration to decrease rapidly, such as postoperative hyponatremia and self-induced water intoxication that develops over a few hours (Table 1). Because the brain cannot swell by much more than 5%, correction of hyponatremia by this amount would be expected to prevent the most serious complications of acute water intoxication; empirical observations support this prediction. An increase in the plasma sodium concentration of 4 to 6 mmol per liter is enough to reverse impending brain herniation or stop active seizures in patients with severe acute hyponatremia. Such an increase can be reliably achieved with 100-ml bolus infusions of 3% saline (2 ml per kilogram in small patients), administered at 10-minute intervals to a total of three doses, if necessary, to control symptoms.[39] Milder symptoms of acute hyponatremia should be treated with enough 3% saline to avoid a worsening of hyponatremia because of delayed absorption of ingested water or excretion of hypertonic urine.[72]

Hyponatremia is usually a chronic condition and it should be presumed to be chronic when the actual duration is unclear; to reduce symptoms and improve potential outcomes, chronic hyponatremia should be corrected gradually with the use of fluid restriction, salt tablets, slow infusions of 3% saline, furosemide, urea, or vasopressin antagonists, or by treatment of the underlying cause. Severe symptoms of hyponatremia may require

Table 2. Treatment and Limits of Correction of Severe Hypernatremia.*

Duration	Related Behavior or Condition	Clinical Features	Initial Therapeutic Goal	Limit of Correction and Management of Overcorrection
Minutes to hours	Acute salt poisoning associated with accidental salt ingestion or salt ingestion in attempted suicide, use of parenteral hypertonic saline, dialysis errors	Seizures, coma, hypertonia, high fever, intracranial hemorrhages, thrombosis of dural sinuses	Rapid infusion of 5% dextrose in water plus emergency hemodialysis to immediately restore normonatremia	Excessive correction not known to be harmful
1–2 days	Unreplaced water from urinary losses associated with glycosuria, neurogenic or nephrogenic diabetes insipidus	Persistent coma, brain demyelination	Decrease plasma sodium concentration by 2 mmol/liter/hr until plasma sodium concentration is 145 mmol/liter; stop or replace water losses	Excessive correction not known to be harmful
Unknown or ≥2 days	In children: diarrhea, inability to breast-feed; in adults: hypodipsia, impaired mental status	Obtundation or coma, rehydration-associated seizures and cerebral edema as a result of rapid correction in children	In children: decrease plasma sodium concentration by 0.3 mmol/liter/hr; in adults: decrease plasma sodium concentration by 10 mmol/liter/day; replace water losses	In children: avoid decreasing plasma sodium concentration by >0.5 mmol/liter/hr; 3% saline for seizures associated with rehydration; in adults: not known

* Severe hypernatremia is defined as a plasma sodium concentration above 150 mmol per liter. In the absence of urinary loss of water, 3 ml of electrolyte-free water per kilogram of body weight will decrease the plasma sodium concentration by approximately 1 mmol per liter.

more aggressive initial interventions, but there is no need to increase the plasma sodium concentration by more than 4 to 6 mmol per liter per day. Regardless of how chronic hyponatremia is treated, inadvertent overcorrection, most commonly caused by excretion of dilute urine, is common and can be very dangerous (see Case 3 in the Supplementary Appendix).[42,43] If the plasma sodium concentration is less than 120 mmol per liter, or if there are risk factors for osmotic demyelination, correction of the plasma sodium concentration by more than 8 mmol per liter per day should be meticulously avoided through replacement of lost water or prevention of water loss with desmopressin, a synthetic vasopressin.[42,73]

Repeat therapeutic lowering of the plasma sodium concentration is justified if the correction of hyponatremia exceeds 8 mmol per liter per day and there are risk factors for osmotic demyelination or if the correction is 10 to 12 mmol per liter per day without these risk factors (Table 1)[39,40,74,75] — although the benefit of this strategy has not been confirmed in humans. To prevent inadvertent overcorrection (see Case 4 in the Supplementary Appendix), desmopressin can be administered preemptively, in anticipation of, rather than in response to, unwelcome urinary losses of water; hyponatremia is corrected with a slow infusion of 3% saline while the urine is kept concentrated with repeated doses of desmopressin.[73]

Limiting correction of chronic hypernatremia so that the plasma sodium concentration is decreased by less than 0.5 mmol per liter per hour reduces the risk of cerebral edema and seizures associated with rehydration.[66] However, the fear of these complications, which have been reported only in young children, should not deter the aggressive rehydration of adults with acute hypernatremia to avoid brain hemorrhage or osmotic demyelination (Table 2).[76] In contrast to the risk of inadvertent overcorrection in patients with hyponatremia, there is little risk of inadvertent overcorrection in patients with hypernatremia, and adults with hypernatremia are often undertreated.[77,78]

CONCLUSIONS

Disorders of plasma sodium concentration expose cells to hypotonic or hypertonic stress. Although all cells are affected, clinical manifestations of hyponatremia and hypernatremia are primarily neurologic, and rapid changes in plasma sodium concentrations in either direction can

cause severe, permanent, and sometimes lethal brain injury. Because the brain adapts to an abnormal plasma sodium level, excessive correction of a chronic disturbance can be injurious and should be avoided.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the author to give readers additional information about his work.

Supplement to: Sterns RH. Disorders of plasma sodium — causes, consequences, and correction. N Engl J Med 2015;372:55-65. DOI: 10.1056/NEJMra1404489

Disorders of Plasma Sodium – Causes, Complications, and Correction

Supplemental Appendix

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Table of Contents

Pathogenesis of Osmotic Demyelination

It is well accepted that rapid changes in the plasma sodium concentration can result in brain demyelination, but the precise mechanism underlying this injury is still under investigation. The discovery of bile pigment in the brains of jaundiced patients who died of central pontine myelinolysis led Norenberg to the idea that osmotically-induced disruption of the blood brain barrier might be the cause of the disorder. [1] This was an attractive hypothesis because it had been shown that a rapid rise in plasma osmolality opens the blood brain barrier (BBB), possibly by shrinking endothelial cells and altering their tight junctions.[2,3]

Norenberg's hypothesis was supported by studies by Baker and co-workers which found that development of demyelination in the rat was associated with magnetic resonance indices of BBB disruption and that IgG and C3d were found after rapid correction of hyponatremia in areas of the brain undergoing osmotic demyelination.[4] Because complement is toxic to oligodendrocytes (the cells in the central nervous system involved in synthesizing, organizing and wrapping myelin around nerves), these findings suggested that a rapid increase in plasma sodium leads to BBB disruption, followed by an influx of complement into the brain, which then results in demyelination.

More recently, Gangkam-Kengne and co-workers found that under some conditions, osmotic opening of the blood brain barrier could be dissociated from subsequent

demyelination and suggested that injury to astrocytes was the primary lesion in osmotic demyelination.[5] Studying the temporal relationship between astrocyte loss and myelin loss in a rat model of osmotic demyelination, these investigators found that astrocyte death precedes demyelination. Astrocytes, the most abundant cell type in the nervous system, regulate water homeostasis in the brain; these cells become depleted of organic osmolytes during the adaptation to hyponatremia, and loss of osmolytes make them more vulnerable to injury from osmotic stress. The foot processes of astrocytes encircle brain capillaries and interact with endothelial cells, oligodendrocytes, and microglia.[6] There is evidence that alterations in astrocyte proteins, such as aquaporins, which regulate water and ion flux, directly affect the ability of oligodendrocytes to maintain myelin structure and integrity.[7] Connexins connect astrocytes to each other and to oligodendrocytes in a network whose integrity is crucial for myelination and remyelination after demyelinative injury.[5,7] In addition, astrocytes play an important role in inducing endothelial cells to form the tight junctions characteristic of the BBB[8] and signaling between astrocytes and endothelial cells can lead to rapid and transient opening of the BBB. [6] Therefore, shrinkage and subsequent apoptosis of astrocytes could explain many of the phenomena that occur after rapid correction of chronic hyponatremia: transient opening of the blood brain barrier, loss of myelin-producing oligodendroytes and proliferation of microglia.

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Case Examples

Case 1

A 57 year old woman with a 20 year history of bipolar disorder treated with lithium undergoes abdominal surgery and is given nothing by mouth beginning at midnight the night before her operation. Two days after surgery she becomes unresponsive. Perioperative input is 6250 ml 5% dextrose in lactated Ringer's solution (sodium concentration 130 mmol per liter), and urine output is 5870 ml. Pre-operative plasma sodium was normal and 24 hours after surgery it is 168 mmol per liter. She is treated with 5% dextrose in 0.45% saline (sodium concentration 77 mmol per liter) at 100 ml per hr and plasma sodium increases to 175 mmol per liter over 8 hours. Urine osmolality is 159 mOsm per kilogram, urine sodium is 36 mmol per liter and urine potassium is 9 mmol per liter.

The patient has nephrogenic diabetes insipidus caused by long-term lithium therapy. Pre-operative plasma sodium was normal because thirst prompted her to replace urinary water losses. Perioperative fluids were nearly isotonic, providing her with almost no electrolyte-free water. Therefore, excretion of dilute urine without water replacement resulted in a rapid onset of severe hypernatremia with neurological symptoms. Treatment with 0.45% saline at 100 ml per hr was inadequate, because only 50 ml per hr of electrolyte-free water was provided, less than half the rate of urinary water losses. A rapid onset of severe hypernatremia risks osmotic demyelination and the plasma sodium should be rapidly re-lowered

with a rapid infusion of 5% dextrose in water, combined with furosemide to eliminate the excess sodium given to her in the intravenous fluids.

Case 2

A 50 year old man is admitted with subarachnoid hemorrhage. He is treated with intravenous 0.9% sodium chloride (sodium concentration 154 mmol per liter) at 200 ml per hr, and plasma sodium gradually falls from normal to 125 mmol per liter. He is then treated with 4.5 liters of intravenous fluid having an average sodium concentration of 300 mmol per liter, and is given nothing by mouth. Despite therapy with hypertonic fluids, plasma sodium does not change. The 24 hour urine output is 4.8 liters, urine osmolality is 625 mOsm per kilogram, urine sodium 263 mmol per liter and urine potassium 24 mmol per liter.

This patient has the syndrome of inappropriate antidiuretic hormone secretion (SIADH) caused by subarachnoid hemorrhage. Vasopressin secreted in response to his acute neurological injury caused the urine to be concentrated (urine osmolality 625 mOsm per kilogram) despite the presence of hypotonic hyponatremia and large amounts of sodium were excreted in the urine because of volume expansion with isotonic saline. The plasma sodium concentration fell because the urine was hypertonic (urine sodium plus potassium concentration equals 287 mmol per liter). The sodium contained in two liters of isotonic saline can be excreted in just over one liter of hypertonic urine; the net effect is positive electrolyte-free water balance, weight gain and hyponatremia. Intravenous fluid with a sodium concentration of

300 mmol per liter was ineffective because the sodium plus potassium concentration of the infusate and its rate of input was nearly matched by the sodium plus potassium concentration of the urine and its rate of output. If urine output continues at its current rate and composition, infusion of 3% saline (sodium concentration 513 mmol per liter) at 100 ml per hour would approximately replace urinary sodium losses, allowing net electrolyte-free water loss which would increase the plasma sodium.

Case 3

A 30 year old woman with von Willebrand's disease is treated with desmopressin before and after cholecystectomy to prevent bleeding. On the third hospital day, she has a major motor seizure. Plasma sodium concentration is 109 mmol per liter, urine osmolality is 325 millisomoles per kg, urine sodium is 114 mmol per liter and urine potassium is 9 mmol per liter. She is treated with 3% saline (sodium concentration 513 mmol per liter) at 100 ml per hour (2 ml per kg body weight per hour) for 5 hours and plasma sodium increases to 119 mmol per liter. During the next eight hours all fluid intake is withheld, the plasma sodium increases to 127 mmol per liter and she becomes fully alert and oriented. A repeat urine osmolality is 100 mOsm per kilogram and urine output is 600 ml per hr. The next day, plasma sodium is 139 mmol per liter. A day later she becomes unresponsive. Spastic quadriparesis and pseudobulbar palsy develops and, after two weeks, magnetic resonance imaging of the brain confirms the diagnosis of osmotic demyelination syndrome. The patient survives, with permanent, severe disabilities.

The patient developed symptomatic hyponatremia due to exogenous antidiuretic hormone (desmopressin). Because of severe symptoms, administration of 3% saline was indicated to increase plasma sodium by 4 to 6 mmol per liter. Absent urinary water losses, an increase of 10 mmol per liter would be expected, because 1 ml of 3% saline per kg body weight should increase the plasma sodium by approximately 1 mmol per liter and she was given 10 ml per kg. However, as the effect of desmopressin wore off and plasma hypotonicity suppressed endogenous vasopressin secretion, the urine became maximally dilute, and the plasma sodium continued to increase owing to urinary water losses. Three days of hyponatremia was sufficient time for brain cells to adapt; the large, rapid increase in plasma sodium (30 mmol per liter in 28 hours) caused osmotic demyelination, with a typical biphasic clinical course, and this resulted in permanent brain damage.

Case 4

A 60 year old man with a history of heavy beer drinking presents with confusion, weakness and falls 10 days after being started on hydrochlorthiazide for the treatment of hypertension. Serum sodium is 104 mmol per liter and serum potassium is 2.5 mmol per liter. Urine osmolality is 650 mOsm per kilogram and urine sodium is 10 mmol per liter. Hydrochlorthiazide is discontinued and he is treated with potassium supplements and 2 micrograms of desmopressin subcutaneously. Over the next six days, repeat doses of desmopressin are given every eight hours and he is also treated with an infusion of 3% saline that is adjusted to achieve a 4 mmol per liter daily increase in plasma sodium. When the

plasma sodium concentration reaches 128 mmol per liter, desmopressin and 3% saline are discontinued. The patient's symptoms resolve and his plasma sodium eventually returns to normal.

The patient has thiazide-induced hyponatremia with several risk factors for developing osmotic demyelination: plasma sodium less than 105 mmol per liter, hypokalemia, and alcoholism. Once the thiazide is discontinued, he is also at risk of developing a spontaneous water diuresis that could result in unintentional rapid correction of hyponatremia. Because of these risks, he was given desmopressin to prevent urinary water losses from developing. Repeated administration of desmopressin creates a state of iatrogenic SIADH and the plasma sodium is increased by administering hypertonic potassium chloride and sodium chloride. The goal of therapy for all patients with severe hyponatremia is a daily increase of 4 to 6 mmol per liter. Because of this patient's added risk factors for developing osmotic demyelination syndrome, a 4 mmol per liter daily target was chosen.