Disorders of Water Metabolism

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INTRODUCTION

Disorders of water metabolism are associated with disturbances of normal plasma osmolality. In clinical practice, these disorders present primarily as problems associated with hyponatremia or, less commonly, hypernatremia. The near-synonymity of disorders of water metabolism with derangement of the normal serum sodium concentration reflects the primacy of sodium as the dominant cation of extracellular fluid (ECF).

To correctly solve problems involving hyponatremia or hypernatremia, one must remember that hormones affecting osmolality respond to changes in plasma osmolality as well as changes, real or perceived, in circulating plasma volume. Many apparent clinical problems arise under conditions in which osmoregulatory hormones are secreted inappropriately with regard to plasma osmolality but entirely appropriately with regard to perceived plasma volume signaling. When addressing problems of hypo- and hypernatremia, it is crucial to recall that when osmolar signaling is at odds with volume signaling, volume signaling is quantitatively (and qualitatively) more dominant.

PHYSIOLOGY OF WATER METABOLISM

Total Body Water and Plasma Osmolality

Total body water (TBW) constitutes approximately 60% of the total body weight in young adult men (50% in young adult women). Older age and higher percentage of body fat correlate with lower TBW as a percentage of body weight. A simple calculation for TBW (in L) is to multiply patient body weight (in kg) by 0.6 (for an adult male), 0.5 (adult female), 0.5 (elderly male), or 0.45 (elderly female).

Roughly two thirds of TBW is contained in the intracellular fluid (ICF) compartment, with one third in the ECF compartment. Movement of water between the ECF and ICF is governed primarily by the osmolality of each compartment. Under normal conditions, ECF osmolality and ICF osmolality are approximately the same. Thus, plasma osmolality is a useful indicator of the osmolality within cells. For practical purposes, plasma osmolality (in mOsm/kg) can be estimated from the concentrations of the major osmotically active ECF solutes using the following formula:

\[ (2 \times \text{Na}^+) + (\text{glucose}/18) + (\text{BUN}/2.8) \]

where sodium (Na\(^+\)) is expressed in mEq/L and glucose and blood urea nitrogen (BUN) are expressed in mg/dL. If BUN and glucose concentrations are normal, plasma osmolality can be estimated using the following simplified formula:

\[ (2 \times \text{Na}^+) + 8 \]

A comparison of estimated versus directly measured plasma osmolality is an important checkpoint prior to initiating therapy for hyponatremia, since instances of pseudohyponatremia may be associated with normal or even elevated plasma osmolality. Directly measured plasma osmolality should agree with estimated plasma osmolality within 20 mOsm/kg; a larger discrepancy suggests the presence of an unmeasured osmole, such as an alcohol, a lipid, or a paraprotein. Although clinical situations featuring osmolar gaps are unusual, the recognition that one is present may lead to a diagnosis of otherwise unsuspected poisoning, for example with ethylene glycol or methanol. Severe hypertriglyceridemia or paraproteinemia should be obvious from measurement of plasma lipids (the serum should appear grossly lipemic) and total protein.

Normal Governance of Plasma Osmolality

Normal plasma osmolality is maintained primarily by a balance of renal excretion and oral intake of water, since daily solute excretion is largely of an obligate nature.

Vasopressin-mediated renal water handling. The dominant osmoregulatory hormone is vasopressin (antidiuretic hormone [ADH]). Vasopressin is synthesized by neurosecretory neurons in the paraventricular and supraoptic nuclei of the hypothalamus and migrates along axons within the pituitary stalk to the posterior pituitary, where it is ready for release in response to osmotic or nonosmotic stimuli.

Vasopressin release is triggered by plasma osmolality as it rises above 288 mOsm/kg. Rising plasma osmolality is perceived by osmoreceptors located in
the anterolateral wall of the hypothalamus, adjacent to the third ventricle; these osmoreceptors in turn signal vasopressin release from the neurohypophyseal axons into the general circulation. Vasopressin exerts its osmoregulatory effects by binding to V2 receptors on the apical membrane of cells in the proximal collecting duct of the nephron, thus inducing the translocation of aquaporin-2 to the apical surface of these cells. Thus activated, aquaporin-2 renders the collecting duct cell permeable to water, which is reabsorbed along interstitial osmolar gradients. The net result of vasopressin–V2 receptor interaction is formation of concentrated urine and reduced plasma/interstitial osmolality. Conversely, vasopressin secretion is profoundly inhibited when plasma osmolality is below 280 mOsm/kg, and in this setting, collecting duct epithelium is water-impermeable; thus, renal free water excretion increases and plasma osmolality rises until the signal threshold for vasopressin is reached again.

There are several important nonosmotic influences on vasopressin secretion. In states of low actual or perceived circulating blood volume, catecholamines and angiotensin II are stimulated and in turn stimulate vasopressin secretion. Thus, as a rule, vasopressin secretion and action will be high in states of intravascular volume depletion (eg, due to blood loss, vomiting, or diarrhea) or in states of reduced effective arterial volume (eg, congestive heart failure [CHF], cirrhosis, nephrotic syndrome). Nonosmotic release of vasopressin is considered a normal part of the human stress response and may occur with significant trauma or nausea and in the postoperative state, among other stressful conditions.

Maximally dilute urine (≤ 100 mOsm/kg) reflects near-absence of vasopressin effect and is the appropriate renal response to serum hypo-osmolality (< 280 mOsm/kg). In this instance, maximally dilute urine reflects the appropriate suppression of vasopressin release by osmoreceptors correctly perceiving the serum hypo-osmolality. At the other extreme, highly concentrated urine (> 600 mOsm/kg) reflects high serum (and renal) vasopressin activity and is the appropriate renal response to serum hyperosmolality (> 290 mOsm/kg). In this instance, hyperconcentrated urine reflects maximal vasopressin effect due to the appropriate signaling of vasopressin release by the osmoreceptors correctly perceiving serum hyperosmolality.

Thirst mechanism. Dipsogenic stimuli arise from the same osmoreceptors of the anterior hypothalamus that signal (or suppress) vasopressin release. The usual set point for thirst is a few mOsm above the set point for maximal vasopressin release; thus, renal water conservation is maximal before ingestion of water is required. Thirst is normally suppressed when plasma osmolality drops below 288 mOsm/kg.

Renal sodium excretion. Aldosterone’s activity is largely dependent on the activity of the renin-angiotensin system, which is activated by reduced arterial perfusion pressure at the level of its sensor organ, the juxtaglomerular apparatus of the afferent renal arteriole. Reduced juxtaglomerular perfusion occurs in states of low real or perceived (effective) arterial volume; thus, true hypovolemia and states of reduced effective arterial volume result in enhanced renin secretion, enhanced angiotensinogen-to-angiotensin II activation, and consequentially, increased aldosterone secretion and action. Under the influence of aldosterone, distal nephron reabsorption of filtered sodium is maximal; the low renal perfusion state that often accompanies (and causes) the hyperaldosteronemic state is also associated with a hormone-independent increase in proximal nephron reabsorption of sodium.

Increased distention of the left ventricle, which would occur normally with expanded plasma volume and abnormally with left ventricular heart failure, results in release of atrial natriuretic peptide (ANP) into the circulation. The effect of ANP on the proximal renal tubule results in increased sodium excretion in the urine. Osmoregulation of ANP, if it exists at all, appears to be minimal and clinically insignificant. ANP secretion and action are profoundly inhibited by states of reduced circulatory volume. By contrast, in edematous states, ANP secretion (and hence, serum levels) are markedly increased, but ANP activity (as assessed by renal sodium excretion) is markedly reduced; thus, edematous states are associated with renal resistance to ANP.

HYPO-OSMOLAR HYponatREMIA

Hypo-osmolar hyponatremia is defined by a measured serum osmolality less than 280 mOsm/kg and a concurrent serum sodium less than 135 mEq/L. Mild hypo-osmolar hyponatremia is the most common electrolyte abnormality in hospitalized patients and is not independently associated with excess morbidity and mortality. However, failure to recognize the underlying abnormalities of renal water handling, deranged Starling forces and/or vasopressin secretion, or inappropriate oral or intravenous water intake places the patient at risk for developing severe hypo-osmolar hyponatremia, which is heralded by neurocognitive dysfunction.
**Table 1. Causes of Hypo-osmolar Hyponatremia**

<table>
<thead>
<tr>
<th>Mechanism of Hyponatremia</th>
<th>Specific Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary polydipsia</td>
<td>Psychogenic water drinking, dipsogenic lesion of hypothalamus, renal salt wasting (diuretics, tubulointerstitial disease, primary adrenal insufficiency [glucocorticoid + mineralocorticoid deficiency]), gastrointestinal fluid losses (vomiting, diarrhea, hemorrhage)</td>
</tr>
<tr>
<td>Intravascular volume depletion</td>
<td>Congestive heart failure, cirrhosis, nephrotic syndrome, syndrome of inappropriate antidiuretic hormone secretion, secondary adrenal insufficiency (glucocorticoid deficiency), hypothyroidism</td>
</tr>
<tr>
<td>Edematous states</td>
<td>Sodium depression syndrome, syndrome of osmotic demyelination includes quadriplegia and pseudobulbar palsy and may be fatal.</td>
</tr>
<tr>
<td>Euvolemic gain of total body water</td>
<td>Congestive heart failure, cirrhosis, nephrotic syndrome, syndrome of inappropriate antidiuretic hormone secretion, secondary adrenal insufficiency (glucocorticoid deficiency), hypothyroidism</td>
</tr>
</tbody>
</table>

**CAUSES**

Table 1 summarizes the major causes of hypo-osmolar hyponatremia, and the Figure outlines a diagnostic approach. When assessing the patient, looking for evidence of volume contraction (poor skin turgor, skin tenting, orthostatic drop in blood pressure and rise in pulse), edema, stigmas of CHF (pulmonary crackles, elevated jugular venous pressure, S), and cirrhosis (positive abdominal fluid wave or shifting dullness, caput medusae, spider angiomata) may elicit clues to the etiology of hyponatremia. Examination of temporally paired serum electrolytes and osmolality and urine osmolality and sodium also provides insight into the pathophysiology.

**CLINICAL FEATURES**

Symptoms are neurocognitive and can range from nausea and vomiting to confusion, disorientation, and ultimately seizures and coma. In hypo-osmolar disorders, cerebral dysfunction is related to osmotic swelling of brain cells—a result of the ICF compartment being hypertonic relative to the surrounding plasma and ECF. Because brain cell swelling is ultimately limited by the skull, neuronal dysfunction is inevitable.

There is no threshold of serum sodium/osmolality at which central nervous system (CNS) dysfunction inevitably occurs; more important clinically is the rapidity of onset. In general, neurocognitive dysfunction is expected when serum sodium is less than 120 mEq/L, possible when serum sodium is less than 128 mEq/L, and is not expected when serum sodium is more than 130 mEq/L. Urgency to correct serum sodium/osmolality is thus dictated not only by the serum sodium value but also by the patient’s neurologic status and the rate of change in serum sodium/osmolality, which can be established by review of serum electrolyte data.

**MANAGEMENT PRINCIPLES**

The first step in managing a recognized case of hypo-osmolar hyponatremia is to assess the sensorium. When CNS malfunction is present (new-onset seizures, delirium, confusion, obtundation, coma, headache, nausea), the implication is that the serum hypo-osmolality has evolved relatively rapidly—and in excess of the brain’s ability to adapt to changing osmolality. When serum hypo-osmolality begins to develop, rapid CNS adaptation includes the active transport of inorganic ions (potassium, sodium, chloride) from the ICF to the ECF. This adaptation begins within hours. When hypo-osmolality persists for more than a few days, brain cells begin to extrude organic osmoles (glutamate, taurine, inositol). This active autoregulation of intracellular brain osmolality is an important defense against the shift of fluid from the ECF to the ICF compartment, which would otherwise cause cerebral edema and neuronal dysfunction due to compression of the swollen brain by the calvarium. Indeed, the manifestations of brain dysfunction are largely attributable to cerebral edema, and when these are present, urgent correction of the plasma hypo-osmolality is indicated.

Conversely, when plasma hypo-osmolality evolves very gradually, CNS compensation is apt to be complete—and the patient nearly asymptomatic. In this case, aggressive and rapid correction of the hypo-osmolality may have dire consequences. The rare but well-documented syndrome of osmotic demyelination includes quadriplegia and pseudobulbar palsy and may be fatal.

**Conservative versus Aggressive Correction**

It is impossible to define exact cutoff points to determine whether treatment should be gradual or rapid, but the following considerations are useful.

**Conservative correction.** If neurologic symptoms are absent or minimal and serum sodium is greater than 125 mEq/L, and urine osmolality is less than 200 mOsm/kg, water restriction (to 800–1000 mL/day) should result in gradual improvement. It is important to account for the water content of foods in the restriction. Effective fluid restriction outside the hospital represents a significant patient adherence challenge, and close follow-up is warranted. The usual goal of therapy is to maintain serum sodium above 128 mEq/L.

**Aggressive correction.** If neurologic consequences of hypo-osmolality are severe (seizures, coma, severely depressed sensorium) and serum sodium is less than 125 mEq/L and urine osmolality is greater than 200 mOsm/kg, aggressive correction is justifiable because fluid restriction alone will not correct the hypo-osmolality or reverse symptoms rapidly enough.
**Disorders of Water Metabolism**

**Case examples with discussion**

**Case 1: Water Intoxication in a Patient with CHF**

A 69-year-old woman suffers a grand mal seizure after completing a urologic ultrasound procedure that required her to ingest 2 L of plain water in less than 2 hours. Her medical history is pertinent for CHF. Medications include digoxin and isosorbide mononitrate.

Physical examination reveals a very lethargic, slow to arouse, nonverbal confusional state. Vital signs are: temperature, 98°F; blood pressure, 130/70 mm Hg; heart rate, 80 bpm; and respiratory rate, 16 breaths/min. Weight is 60 kg. The neurologic examination is nonfocal. Chest auscultation reveals basilar crackles in both lung fields and an S3 gallop. There is 3-mm pitting edema of both legs to mid-shin.

Results of laboratory studies include: serum sodium, 118 mEq/L (normal, 136–144 mEq/L); serum potassium, 3.8 mEq/L (normal, 3.5–5.0 mEq/L); serum chloride, 82 mEq/L (normal, 100–110 mEq/L); serum bicarbonate, 24 mEq/L (normal, 22–28 mEq/L); BUN, 30 mg/dL (normal, 8–20 mg/dL); serum creatinine, 1.1 mg/dL (normal, 0.4–1.4 mg/dL); serum glucose, 84 mg/dL (normal, 60–99 mg/dL); urine osmolality, 450 mOsm/kg (physiologic range, 50–1200 mOsm/kg); and urine sodium, 8 mEq/L (physiologic range, < 5 to > 40 mEq/L).

- **What mechanisms likely account for this patient’s seizure and hyponatremia, and how should she be treated?**

**Pertinent Pathophysiology in this Case**

This woman’s clinical history and physical examination document underlying CHF, which may have been somewhat decompensated at the time of her urologic procedure. Edematous states are associated with concurrent expansion of the ECF and reduced effective arterial volume. In CHF, there is profound neurohumoral activation of the sympathetic nervous system and the renin-angiotensin system and, hence, increased...

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**Figure.** Diagnostic approach to the patient with hypo-osmolar hyponatremia. GI = gastrointestinal; SIADH = syndrome of inappropriate antidiuretic hormone secretion.
circulating levels of catecholamines (particularly nor-
epinephrine), angiotensin II, and aldosterone. Natri-
uretic peptides are appropriately elevated but response
is suboptimal, owing to the more powerful influence of
the other hormones. The net effect of the hormonal
milieu in this state is profound sodium retention. Thus,
patients with CHF (and other edematous states) usually
have hypo-osmolar hyponatremia, edema and/or ascites,
prerenal azotemia (BUN:creatinine ratio > 20), less
than maximally dilute urine (usually > 300 mOsm/kg
in the absence of diuretic therapy), and very low urine
sodium (< 20 mEq/L). Concentrated urine with low
urine sodium is the sine qua non of an actual or a func-
tional hypovolemic state.

In CHF, the nonosmotic influences of norepineph-
rine and angiotensin II stimulate thirst and vasopressin
secretion. Given the increased vasopressin effect, the
case patient was unable to appropriately excrete an
acute free water load and easily developed hyponatremic
water intoxication. Her seizure occurred due to acute
cerebral edema, which was the result of osmotic shift of
water from the suddenly hypotonic ECF compartment
to the relatively hypertonic ICF compartment.

Treatment Considerations

This patient meets the criteria for aggressive correc-
tion of her hypo-osmolality. In this case, several treat-
ment considerations apply.

Administration of a loop diuretic (eg, furosemide)
intravenously is warranted if the urine osmolality ex-
ceds 300 mOsm/kg. Because these agents impair
urinary concentrating capacity, their use should re-
duce urine osmolality to approximately that of normal
plasma.

Administration of hypertonic (3%) saline solution
can be used to correct hypo-osmolality in a reasonably
precise fashion, if the volume of infusate is calculated
according to the following formula, which estimates the
increment in serum sodium per L of infusate (for 3%
saline, the infusate sodium is 513 mEq/L; for normal
[0.9%] saline, the infusate sodium is 154 mEq/L):

\[
\text{Change in serum Na}^+ = \frac{\text{infusate Na}^+ - \text{serum Na}^+}{\text{TBW} + 1}
\]

The goal of hypertonic saline infusion therapy is
to effect a partial correction of serum sodium to
125 mEq/L during the first 24 hours, at a rate not to ex-
ced 1 to 2 mEq/hr. Rates of correction in excess of this
have been associated with the osmotic demyelination
syndrome.

Applying the above formula to the case patient,
TBW would first be estimated as 27 L (60 kg × 0.45).
Then, if hypertonic (3%) saline is used as the correction
infusate:

\[
\text{Change in serum Na}^+ = \frac{513 \text{ mEq/L} - 118 \text{ mEq/L}}{27 \text{ L} + 1} = 14 \text{ mEq/L increment in serum Na}^+ \text{ per L of infusate}
\]

Based on this calculation, serum sodium should be
expected to rise by about 1 mEq/L for every 71 mL of
infusate administered. In practice, hypertonic saline
is usually administered at a rate of 40 to 60 mL/hr
to avoid overly rapid correction. Serum electrolytes
should be measured regularly (every 2–4 hours), and
the hypertonic infusate should be stopped when the
serum sodium reaches 125 mEq/L.

Case 2: Acute Water Intoxication in a Psychiatric
Patient

A 50-year-old woman hospitalized for schizophrenia
on a psychiatric unit develops extreme obtundation
requiring emergent medical evaluation. Aside from
her psychiatric condition, the patient’s only notable
medical history is hypertension, which was diagnosed
in the previous year and is being treated with a thia-
zide diuretic. On physical examination, there is no
edema, the chest is clear to auscultation, and heart
sounds are limited to a normal S\textsubscript{1} and S\textsubscript{2}, with no
murmur or gallop. Weight is 72 kg. Blood pressure is
128/70 mm Hg, heart rate is 70 bpm, and respiratory
rate is 14 breaths/min.

Results of laboratory studies include: serum sodium,
108 mEq/L; serum potassium, 3.4 mEq/L; serum chlo-
ride, 72 mEq/L; serum bicarbonate, 24 mEq/L; BUN,
4 mg/dL; serum creatinine, 0.6 mg/dL; serum glucose,
72 mg/dL; serum uric acid, 12 mEq/L; urine osmolal-
ity, 250 mOsm/kg; and urine sodium, 50 mEq/L.

- What mechanisms likely account for this patient’s se-
vere hyponatremia, and how should she be treated?

Pertinent Pathophysiology in this Case

Several diagnostic possibilities must be considered
in a psychiatric patient who presents with hyponatre-
ia. From 6% to 7% of psychiatric inpatients may have
compulsive water drinking, and up to half of these
patients can have symptomatic hyponatremia. High
oral fluid intake profoundly suppresses vasopressin, re-
sulting in copious amounts of dilute urine (osmolality
< 100 mOsm/kg). History of compulsive water drink-
ing should be sought in the evaluation of this patient.
Thiazide diuretics impair renal diluting capacity—a property that is exploited in the treatment of nephrogenic diabetes insipidus. By impeding the ability to excrete free water, thiazide diuretics may set the stage for the development of symptomatic hypo-osmolar hyponatremia if patients habitually ingest large amounts of free water.\textsuperscript{9}

Finally, many commonly used antipsychotic agents directly or indirectly stimulate vasopressin secretion, thirst, or both.\textsuperscript{10,11} Older antipsychotic agents (eg, phenothiazines) have anticholinergic side effects such as dry mouth, which would provide stimulus to drink. Direct effects of antipsychotic agents on vasopressin secretion are known to cause or contribute to the syndrome of inappropriate ADH secretion (SIADH).

Serum uric acid can be helpful in the differential diagnosis of hypo-osmolar hyponatremia. In disorders associated with net gain of pure water (including SIADH), serum uric acid is usually less than 4 mg/dL, due to dilution of uric acid concentration in the expanded ECF and plasma volume and to increased urinary excretion of uric acid in volume-expanded states.\textsuperscript{12} By contrast, serum uric acid concentration greater than 4 mg/dL may be seen in cases of thiazide diuretic–induced hyponatremia, due to reduced urate clearance in the volume-contracted state. Thus, in the case example, the combination of the thiazide diuretic and excessive intake of solute-poor fluids (due to psychois-related compulsive water drinking) likely accounts for the patient’s severe hyponatremia.

**Treatment Considerations**

This patient’s clinical history and severity of change in mental status justify aggressive correction of hyponatremia, with a goal of improving the serum sodium to 125 mEq/L within the next 24 hours. Hypertonic (3%) saline is a reasonable means of achieving this goal. The standard formula can be used to estimate the rate of intravenous infusate to be administered safely and effectively. In this patient, TBW would be estimated as 43 L (72 kg \times 0.6).

\[
\text{Change in serum Na}^+ = \frac{513 \text{ mEq/L} - 108 \text{ mEq/L}}{43 \text{ L} + 1} = 9 \text{ mEq/L increment in serum Na}^+ \text{ per L of infusate}
\]

Thus, a 1 mEq/L rise in serum sodium is expected for every 110 mL of hypertonic saline infused. To reach the target serum sodium of 125 mEq/L in 24 hours (an increment of 17 mEq/L), approximately 1.9 L of hypertonic saline must be administered. Serum sodium should be monitored every 2 to 4 hours to avoid over- or undercorrection.

### Case 3: Hypopituitarism with Hypo-osmolar Hyponatremia

A 50-year-old man is referred to an endocrinologist for evaluation of symptoms of severe fatigue, loss of libido, and erectile dysfunction. The patient’s symptoms began over a period of 12 to 18 months. On physical examination, blood pressure is 100/60 mm Hg, and pulse is 64 bpm; neither measurement changes significantly with upright posture. The patient’s general appearance is remarkable for sallow skin. Relative to most normal adult men, his body hair in the axillary and pubic regions appears somewhat diminished.

Results of routine laboratory studies include: serum sodium, 128 mEq/L; serum potassium, 3.4 mEq/L; serum chloride, 92 mEq/L; serum bicarbonate, 24 mEq/L; BUN, 10 mg/dL; serum creatinine, 0.7 mg/dL; serum glucose, 64 mg/dL; urine osmolality, 320 mOsm/kg; and urine sodium, 24 mEq/L.

Evaluation of the patient’s pituitary and selected target endocrine gland function reveals the following: thyroid-stimulating hormone (TSH), 0.42 mcU/mL (normal, 0.35–4.5 mcU/mL); free thyroxine (FT\(_4\)), < 0.4 ng/dL (normal, 0.7–1.7 ng/dL); total testosterone, 100 ng/dL (normal [male], 300–1000 ng/dL); lutetizing hormone, 2.3 mU/L (normal, 2–10 mU/L); follicle-stimulating hormone, 3.5 mU/L (normal, 5–10 mU/L); and cortisol, 3.2 µg/dL at baseline and 9 µg/dL 1 hour following administration of 250 µg of cosyntropin (a subnormal response).

Based on the above findings, a pituitary tumor is suspected, which is confirmed on sellar magnetic resonance imaging.

- **What endocrine disorders can cause hyponatremia, and how should they be treated?**

### Hyponatremia Secondary to Endocrine Disorders

Anterior pituitary hormones that have a direct bearing on osmoregulation are thyrotropin and adrenocorticotropic hormone (ACTH); deficiencies of these hormones lead to secondary hypothyroidism and secondary hypocortisolism, respectively. Hypothyroidism (primary or secondary) can be associated with euvoletic hyponatremia, due primarily to reduced glomerular filtration rate and decreased renal plasma flow, which consequently leads to reduced delivery of glomerular filtrate to the distal diluting sites of the nephron.\textsuperscript{13} Hypocortisolism (due to ACTH deficiency or primary adrenal insufficiency) is associated with nonosmolar vasopressin release in response to postural hypotension, nausea, and/or hypoglycemia. Cortisol deficiency also has a direct effect on the distal nephron, impairing urinary dilution. Primary
adrenal insufficiency causes mineralocorticoid as well as glucocorticoid deficiency, and in the presence of the former renal salt wasting occurs, further exacerbating the hyponatremia. Mineralocorticoid deficiency is not seen in the pure glucocorticoid deficiency associated with hypopituitarism and would not be expected in this case.

**Treatment Considerations**

Severe hyponatremia associated with thyroid, adrenal, and pituitary disease can be corrected, but this is usually unnecessary unless acute water loading has occurred as a result of medical treatment or based on unusual patient circumstances. Appropriate therapy includes levothyroxine for primary and secondary hypothyroidism, glucocorticoid for secondary adrenal insufficiency, or glucocorticoid plus mineralocorticoid in the case of primary adrenal insufficiency.

**Case 4: Postoperative Water Intoxication**

A 60-year-old woman becomes confused and disoriented 1 day following hip replacement surgery. She is alert but responds inappropriately to most questions. The patient takes amloidipine for hypertension. Postoperatively, she has been receiving morphine via a patient-controlled analgesia pump; she also has been given promethazine injections twice for nausea. Physical examination is generally normal. Blood pressure is 130/80 mm Hg, and pulse is 72 bpm, without significant change upon standing. Skin turgor is good.

Results of laboratory tests include: serum sodium, 118 mEq/L; serum potassium, 3.3 mEq/L; serum chloride, 82 mEq/L; serum bicarbonate, 24 mEq/L; BUN, 6 mg/dL; serum creatinine, 0.4 mg/dL; serum glucose, 85 mg/dL; serum uric acid, 1.8 mEq/L; urine osmolality, 250 mOsm/kg; and urine sodium, 45 mEq/L.

Results of select endocrine function studies include: serum TSH, 2.2 mcU/mL; serum FT₄, 1.10 ng/dL; and serum cortisol, baseline, 9.0 µg/dL, and 1 hour following injection of 250 µg cosyntropin, 25 µg/dL.

- Why is this patient’s urinary sodium excretion high relative to her severe hyponatremia, and how should this patient be treated?

**Euvolemic Hypo-osmolar Hyponatremia**

This patient fulfills all diagnostic criteria for SIADH: (1) plasma hypo-osmolality with hypo-osmolar hyponatremia; (2) urine osmolality inappropriately high for the plasma osmolality; (3) absence of significant edema, ascites, and orthostatic change in blood pressure or pulse; (4) normal thyroid, adrenal, and kidney function and absence of diuretic use; and (5) absence of avid renal sodium retention.  

This final criterion demonstrates an essential point about SIADH: vasopressin is responsive to both osmolar and nonosmolar stimuli (ie, effective arterial blood volume). In contrast, renal sodium handling responds only to volume-perceived signals mediated through the renin-angiotensin-aldosterone system. SIADH by definition is a condition of slightly expanded effective arterial volume. Thus, the renin-angiotensin-aldosterone system is suppressed, and ANP is stimulated; the net result is enhanced renal sodium excretion. Because patients with SIADH are functionally euvolemic, sodium excretion, which reflects volume status, should be high even though serum sodium and osmolality are abnormally low.

Causes of SIADH are numerous (Table 2), so diagnosis is simply a beginning point. A working differential diagnosis should include CNS disorders, intrathoracic disorders (which may be associated with nonosmolar vasopressin release), and medications (eg, major tranquilizers, narcotics). In the case of a postoperative patient, nonosmotic causes of vasopressin release can include nausea and blood loss; morphine and phenothiazine antiemetics may exacerbate vasopressin production.

**Treatment Considerations**

Severe, acute hypo-osmolar hyponatremia associated with severe neurocognitive dysfunction should be treated as in Cases 1 and 2. When hyponatremia is less severe and chronic, the traditional treatment of first
choice is oral fluid restriction. Given the water content of foods, this often means beverage restriction to less than 1200 mL/day. If this management strategy fails or the patient is unable to comply with such a stringent fluid restriction, additional pharmacotherapy may be necessary. Demeclocyline at a dose of 250 to 500 mg twice daily induces a state of vasopressin resistance (nephrogenic diabetes insipidus), which can be advantageous in a case of SIADH. This therapy is preferable to the pharmacologic alternative, lithium carbonate, due to overall side effect profile. Demeclocycline should be avoided in patients with severe renal and liver disease and in patients with a history of allergy to tetracycline drugs. The newest drug option for treatment of SIADH is conivaptan, a nonselective V1/V2 receptor antagonist. The U.S. Food and Drug Administration has recently approved an intravenous formulation, which is given as a 20-mg loading dose over 30 minutes, followed by 20 mg intravenously over 24 hours for up to 4 days. Additional V2 receptor antagonists are likely to be clinically available within the next several years.

**Table 3. Common Causes of Hypernatremia**

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<th>Defective osmoreceptor function</th>
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<td>Hypothalamic tumors or infarction</td>
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<td>Infiltrative lesions (neurosarcoidosis, histiocytosis X)</td>
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<tr>
<th>Defective vasopressin release</th>
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<td>Complete or partial central DI</td>
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<th>Abnormal nephron</th>
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<td>Acute or chronic renal failure</td>
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<td>Nephrogenic DI</td>
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<th>Abnormal thirst response</th>
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<td>Pharmacologic sedation</td>
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<td>Advanced age</td>
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<td>Impaired cognition</td>
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<td>Psychosocial isolation</td>
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<td>Neurologic/orthopedic impairment</td>
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<th>Gastrointestinal fluid loss</th>
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<td>Severe diarrhea</td>
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<td>Bowel obstruction</td>
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<td>Protracted vomiting illness</td>
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DI = diabetes insipidus.

**HYPEROSMOLAR HYPERNATREMIA**

Hypernatremia is defined by a serum sodium concentration greater than 144 mEq/L. The presence of hyperosmolar hypernatremia implies a significant deficit of TBW relative to total body sodium, which in most cases results from a net loss of water. The earliest adaptive response to the rising plasma osmolality that accompanies water loss is the stimulation of hypothalamic osmoreceptors, which in turn signal vasopressin release. Through its action on V2 receptors in the renal collecting duct, vasopressin should induce a state of avid renal water conservation, manifesting as minimal hourly urine volume (< 50 mL/hr) and maximal urine concentration (up to 1200 mOsm/kg). As plasma osmolality rises by a few additional mOsm, the osmoreceptors also stimulate thirst receptors maximally, causing oral fluid intake until osmolality corrects to below the set point for thirst.

Normal defenses against hyperosmolality are critically dependent on normal osmoreceptor function, normal vasopressin release and suppression, a functionally normal nephron unit with normal V2 receptors for vasopressin, normal thirst response to hyperosmolar signaling, access to drinking water, and normal gastrointestinal water handling. Considering that the host defense against plasma hyperosmolality is twofold (vasopressin and thirst), hypertonic hypernatremia can occur only if either or both mechanisms are defective or overwhelmed by circumstances.

**CAUSES**

Common defects that cause hyperosmolar hypernatremia are shown in Table 3. Clinical history and physical examination should always point toward identification of a source of water loss, which could be sweat loss (eg, high fever, strenuous exertion, hot climate), renal loss (eg, nephrogenic diabetes insipidus), or gastrointestinal loss (eg, diarrhea). If there is no plausible source of net fluid loss, a defective thirst mechanism or poor ability to access drinking water (eg, neurologic or orthopedic disorder, psychosocial deprivation) or central or nephrogenic diabetes insipidus must be inferred and sought by appropriate testing of serum and urine osmolality and sodium.

**CLINICAL FEATURES**

Clinical evidence of intravascular volume depletion (eg, poor skin turgor, skin tenting, orthostatic hypotension and tachycardia) invariably accompany severe cases of hyperosmolar hypernatremia. As serum osmolality exceeds 320 mOsm/kg, impaired neurocognitive function is likely, with manifestations ranging from confusion to stupor and coma.

**MANAGEMENT PRINCIPLES**

The most urgent treatment requirement is to correct the water deficit. As for hypo-osmolar hyponatremia, the...
correction of hypernatremia must not be too rapid. In the case of hyperosmolality, brain cells adapt by actively retaining intracellular inorganic and, later, organic solute.\textsuperscript{17} If plasma osmolality is corrected too rapidly, cerebral edema can occur.\textsuperscript{18} A rule of thumb is to replace gross intravascular volume depletion with 1 to 2 L of isotonic (0.9\%) saline, followed by ongoing replacement of dilute fluids such as 0.45\% saline or 5\% dextrose in water.

**CASE EXAMPLES WITH DISCUSSION**

**Case 1: Osmotic Diuresis with Dehydration Due to Decompensated Diabetes Mellitus**

A 75-year-old woman with a history of type 2 diabetes mellitus (for which she takes glipizide) and Alzheimer’s disease is brought to the hospital for severe obtundation. The woman is a nursing home resident who has become sleepier than usual for the past 72 hours. She appears emaciated, with tenting skin folds. Oral mucosa appears markedly dry. Vital signs include a temperature of 101.5\°F, blood pressure of 90/60 mm Hg, pulse of 112 bpm, and weight of 50 kg. The general physical examination is otherwise normal, and the neurologic examination is nonfocal.

Results of laboratory studies include: serum sodium, 164 mEq/L; serum potassium, 5.2 mEq/L; serum chloride, 122 mEq/L; serum bicarbonate, 30 mEq/L; BUN, 54 mg/dL; serum creatinine, 1.7 mg/dL; serum glucose, 720 mg/dL; urine osmolality, 1050 mOsm/kg; and urine sodium, 45 mEq/L.

- **What factors are contributing to this patient’s hypernatremia, and what is the best management of her condition?**

**Pertinent Pathophysiology in this Case**

This patient clearly has clinical evidence of severe water loss. In large part, her water deficit is attributable to osmotic diuresis from uncontrolled hyperglycemia with glycosuria, but other factors are likely contributing. Alzheimer’s disease might be expected to impair her appreciation of thirst and her ability to act on appropriate dipsogenic signals from the hypothalamic osmoreceptors.\textsuperscript{19} Additionally, as a nursing home resident, her ability to move from bed and chair to obtain drinking water may be impaired.\textsuperscript{20} It is possible that she also has increased insensible sweat–related water loss due to a febrile illness, which in an institutionalized patient would commonly be a urinary tract infection or pneumonia.

**Treatment Considerations**

A common error in treating hypernatremic patients who are severely hyperglycemic is to rely excessively on insulin treatment and to inadequately treat with fluid resuscitation. When frank hypotension or shock is present, the initial fluids used in resuscitation should be isotonic with plasma (typically about 2 L of normal saline or lactated Ringer’s solution), followed by administration of hypotonic fluids at a rate sufficient to gradually correct the serum sodium toward normal. The same formula used to estimate the rate of correction of hyperosmolality can be used to estimate the rate of hypotonic fluid administration in hyperosmolar hypernatremia.

For hypotonic infusate choices, half-normal (0.45\%) saline has a sodium concentration of 77 mEq/L, quarter-normal (0.2\%) saline has a sodium concentration of 34 mEq/L, and 5\% dextrose has a sodium concentration of 0. A pragmatic choice of infusate for the case patient would be 0.45\% saline. Based on the patient’s age and weight, her estimated TBW would be 22.5 L (50 kg × 0.45). Then, using the formula above:

\[
\text{Change in serum Na}^+ = \frac{77 \text{ mEq/L} - 164 \text{ mEq/L}}{22.5 \text{ L}}
\]

\[
= -4 \text{ mEq/L per L of infusate}
\]

One also must factor in the need for 1.5 to 2 L of infusate per 24 hours to allow for ongoing daily obligatory water loss and for correction of hypernatremia at a rate of 1 mEq/L/hr, not in excess of 10 mEq/L per 24 hours.\textsuperscript{21} In this case, 4.5 to 5 L of 0.45\% saline in the first 24 hours should meet the needs for correction of the initial serum sodium from 164 mEq/L to 154 mEq/L and allow for oblige ongoing water loss in the same time period. Thus, for the case patient, the calculated rate of infusion would be 180 to 200 mL/hr of 0.45\% saline solution in the first 24 hours.

**Case 2: Hypernatremia Following Pituitary Surgery**

A 45-year-old woman presents to the emergency department with nausea and anorexia 5 days after hospital discharge. The patient had been hospitalized for 1 week following a trans-sphenoidal resection of a non-secretory pituitary macroadenoma. During the first 24 hours after surgery she had exhibited transient diabetes insipidus, but she then appeared to be overtreated with desmopressin, which was discontinued when her serum sodium reached 128 mEq/L. Serum sodium on the day of hospital discharge was 140 mEq/L.

On physical examination the patient is afebrile, with a blood pressure of 100/60 mm Hg and pulse of 72 bpm. Neurologic examination is nonfocal.

Results of laboratory studies include: serum sodium, 155 mEq/L; serum potassium, 4.5 mEq/L; serum chloride, 119 mEq/L; serum bicarbonate, 24 mEq/L;

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D i s o r d e r s  o f  W a t e r  M e t a b o l i s m
BUN, 24 mg/dL; serum creatinine, 0.9 mg/dL; serum glucose, 72 mg/dL; urine osmolality, 150 mOsm/kg; and urine sodium, 8 mEq/L.

- **What is the patient’s diagnosis, and how should it be managed?**

**Diagnosis and Treatment**

This patient’s postoperative course after pituitary surgery suggests the triphasic response of transient central diabetes insipidus (secondary to transient neurohypophyseal dysfunction), followed by inappropriate antidiuresis (secondary to leakage of preformed vasopressin from damaged neurohypophyseal cell bodies), followed finally by permanent central diabetes insipidus (due to near-total loss of neurohypophyseal function).22,23 A minor gastrointestinal ailment probably impaired this patient’s compensatory water drinking behavior, allowing the unmasking of the central diabetes insipidus.

Correction of the hypernatremia can be accomplished using hypotonic intravenous fluids at a rate calculated as in the prior case example. Additional definitive treatment of this patient’s central diabetes insipidus could include desmopressin (an analog of arginine vasopressin) at a dose of 0.1 mg orally once or twice daily and titrated (according to effect on nocturia and plasma and urine osmolality) up to a dose of 0.8 mg/day in divided doses.24 In the author’s experience, a trial of once-daily dosing at bedtime affords sleep uninterrupted by nocturia but allows a breakthrough period of polyuria late in the waking day. Allowing this therapeutic breakthrough prevents iatrogenic hyponatremia, which can result in serious sequelae (eg, seizures). Other treatment options include thiazide diuretics (which impair renal diluting capacity, raising urine osmolality to approximately 300 mOsm/kg and reducing urine volume to < 5 L) and vasopressin secretagogues, such as chlorpropamide or carbamazepine.25

**Approach to Diagnosis of Polyuria**

**Case Presentation**

A 35-year-old man with a history of pulmonary sarcoidosis complains that over the past 3 months his sleep has been interrupted each night by 4 to 5 episodes of nocturia. He also believes his daytime urinary frequency has increased. The patient habitually drinks ice water when he wakes at night, describing a “cotton mouth” sensation of extreme thirst. He describes his urine as typically being very clear in color. Vital signs and general physical examination are normal.

Serum chemistry panel reveals the following: sodium, 142 mEq/L; potassium, 4.6 mEq/L; chloride, 108 mEq/L; bicarbonate, 24 mEq/L; BUN, 18 mg/dL; and creatinine, 1.0 mg/dL. First-morning voided urine shows an osmolality of 180 mOsm/L and a sodium concentration of 24 mEq/L.

- **What is the logical next step in this patient’s evaluation?**

**Confirm Presence of Polyuria**

This patient’s clinical history suggests central or nephrogenic diabetes insipidus (either of which may be associated with sarcoidosis), but this diagnosis must be proven by measuring the patient’s daily urine volume. Polyuria is defined as a urine volume exceeding 2500 to 3000 mL/24 hr; most patients with symptoms have urine volumes far in excess of that amount. A second pragmatic point is to exclude osmotic diuresis due to uncontrolled diabetes mellitus. In this case, the patient’s urine osmolality and normal serum glucose rule out significant glycosuria. Otherwise, a simple urine dipstick negative for glucose would rule out diabetes.

**Case Continued**

The patient’s 24-hour urine volume is 5500 mL.

- **After confirming that polyuria is present, what is the next step in the diagnosis?**

**Differential Diagnosis of Diabetes Insipidus**

Based on the absence of osmotic diuresis and the presence of polyuria, some form of diabetes insipidus is assured. Dipsogenic diabetes insipidus (primary polydipsia) can result from a hypothalamic lesion, psychiatric disease (compulsive water drinking), or medications that cause uncomfortably dry mouth due to anticholinergic side effects.27 Regardless of cause, dipsogenic diabetes insipidus is characterized by slight plasma hypoosmolality and, thus, slight hyponatremia (serum sodium < 140 mEq/L). Vasopressin is appropriately suppressed, resulting in maximally dilute urine and, thus, maximal renal free water excretion. The case patient’s serum sodium of 142 mEq/L makes dipsogenic diabetes insipidus unlikely27; thus, the diagnosis is either central or nephrogenic diabetes insipidus.

In both central and nephrogenic diabetes insipidus, thirst is compensatory. Given the higher osmoreceptor set point for thirst, plasma osmolality is slightly higher than normal, and serum sodium is normal or slightly

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above normal. Due to the absence of vasopressin effect, both obligate daily water intake and daily renal free water excretion are high.

- How does one distinguish between central and nephrogenic diabetes insipidus?

**UTILITY OF THE WATER DEPRIVATION TEST**

The next step in diagnosing the case patient’s diabetes insipidus is to eliminate his compensatory water drinking by performing a water deprivation test. In a suspected severe case of diabetes insipidus, close monitoring is indicated. The protocol for testing is as follows: (1) the patient is allowed no food or beverage by mouth, and intravenous fluids are withheld; (2) orthostatic blood pressure and pulse are measured hourly; and (3) serum and urine osmolality and serum electrolytes are measured at least every 2 hours. Endpoints for the water deprivation test include: (1) loss of 3% of baseline weight, (2) significant orthostatic blood pressure and/or pulse changes (in either circumstance, there will be nonosmotic stimuli for vasopressin secretion based on hypovolemic signaling), or (3) serum osmolality greater than 300 mOsm/kg and/or serum sodium greater than 145 mEq/L and urine osmolality less than 400 mOsm/L. When an endpoint is reached, aqueous pitressin in a dose of 5 units is administered subcutaneously. Urine osmolality is measured 2 hours later; a rise of greater than 50% above baseline confers a diagnosis of central diabetes insipidus, whereas a rise of less than 10% above baseline confers a diagnosis of nephrogenic diabetes insipidus (ie, proves resistance to the effects of vasopressin).

**CASE CONCLUSION**

The patient’s urine osmolality does not increase after administration of aqueous pitressin, thus establishing a diagnosis of nephrogenic diabetes insipidus. Preferred therapy for this condition is a thiazide diuretic, which potentiates proximal tubular reabsorption of sodium and water, thereby limiting delivery of solute to the distal diluting site and water to the collecting duct. The patient is therefore treated with hydrochlorothiazide 50 mg daily, with reduction in daily urine volume to 3200 mL and relief of his cardinal symptom of nocturia.

**REFERENCES**