Fluid, Electrolyte, and Acid-Base Disturbances

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and Michael Emmett, MD

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Preface

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EDUCATION: Medical and nephrologic information continually accrues at a rapid pace. Bombarded from all sides with demands on their time, busy practitioners, academicians, and trainees at all levels are increasingly challenged to review and understand all this new material. Each bimonthly issue of NephSAP is dedicated to a specific theme, i.e., to a specific area of clinical nephrology, hypertension, dialysis, and transplantation, and consists of an editorial, a syllabus, self-assessment questions, and core nephrology questions to serve as a self-study device. Over the course of 24 months, all clinically relevant and key elements of nephrology will be reviewed and updated. The authors of each issue digest, assimilate, and integrate key publications from the previous issues of other years and integrate this new material with the body of existing information.

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Editorial

What Do Nephrologists Need to Know about Stewart's Method of Acid-Base Analysis?
Asghar Rastegar

Syllabus

Fluid, Electrolyte, and Acid-Base Disturbances
Richard H. Sterns, Michael Emmett, Stanley Goldfarb

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Michael J. Choi, MD and Linda F. Fried, MD
September 2013

Transplantation
David J. Cohen, MD and John P. Vella, MD
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Vaso-Occlusive Disorders and Kidney Disease
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Glomerular, Vascular, and Tubulointerstitial Diseases
Richard J. Glassock, MD and Patrick H. Nachman, MD
May 2014
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Editorial
What Do Nephrologists Need to Know about Stewart’s Method of Acid-Base Analysis?

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Nephrologists have traditionally analyzed acid-base disorders by using the bicarbonate-based method, initially developed by Henderson and Hasselbalch and expanded and modified by many investigators over the past century. One major modification was introduction of base excess (BE) and base deficit used to quantify the degree of metabolic contribution to the disorder. Nephrologists, however, did not widely accept this mechanism(s) underlying the disorder. In 1978, in response to these criticisms, biochemist Peter Stewart used fundamental physical concepts to propose an approach based on charge differences between strong ions in plasma (1). Although this was not a new concept, this method was brought to the bedside by several investigators as a new approach that is both quantitative and mechanistic in nature (2). This approach has gained a good deal of acceptability among anesthesiologists and intensivists (3). As nephrologists, we commonly interact with these colleagues around patients with complex acid-base disorder. To have a productive interaction, it is important that we have adequate familiarity with Stewart’s approach. In this editorial, I initially describe Stewart’s method and compare and contrast it with the bicarbonate-based (traditional) method. The remainder of the article focuses primarily on the clinical utility of Stewart’s method.

Stewart’s Method of Acid-Base Analysis

To understand Stewart’s method, we begin by applying the law of electrical neutrality to plasma and derive the following formula:

\[(\text{Na}^+) + (\text{K}^+) + (\text{Ca}^{2+}) + (\text{Mg}^{2+})] - (\text{Cl}^- + \text{lactate + other strong anions}) - ([\text{HCO}_3^-] + [\text{A}^-]) = 0,\]

where A^- is the base of the weak acids [HA], primarily albumin and to a lesser extent phosphate. This formula can be rearranged as follows:

\[(\text{Na}^+) + (\text{K}^+) + (\text{Ca}^{2+}) + (\text{Mg}^{2+})] - (\text{Cl}^- + \text{lactate + other strong anions}) = ([\text{HCO}_3^-] + [\text{A}^-]).\]

Strong ion difference (SID) is defined as the difference between strong cations and anions, as follows:

\[\text{SID} = (\text{Na}^+) + (\text{K}^+) + (\text{Ca}^{2+}) + (\text{Mg}^{2+})] - (\text{Cl}^- + \text{lactate + other strong anions}) = [\text{HCO}_3^-] + [\text{A}^-].\]

Under normal conditions, concentration of lactate and other strong ions is very low and can be ignored. The formula could therefore be simplified to:

\[\text{SID} = (\text{Na}^+) + (\text{K}^+) + (\text{Ca}^{2+}) + (\text{Mg}^{2+})] - [\text{Cl}^-] = [\text{HCO}_3^-] + [\text{A}^-].\]

The fundamental underpinning of Stewart’s method is the concept that hydrogen ion concentration [H^+] is regulated by three independent variables, namely SID, total weak acids ([A_TOT] = [A^-] + [HA]), and carbon dioxide ([CO_2]). Stewart defined independent variables as “... Those (variables) which can be directly altered from outside the system without affecting each other” and “... dependent variables in a system can be thought of as internal to the system. Their values represent the system’s reaction to the externally imposed values of
the independent variables” (1). This concept is based on mathematical derivation of hydrogen ion concentration in a fluid compartment containing strong ions as well as bicarbonate and carbon dioxide. Using principals of conservation of mass, electrical neutrality, and dissociation constant of partially dissociated weak electrolytes, Stewart derived the following polynomial formula:

\[
\begin{align*}
[H^+]^4 + [H^+]^3(K_a + [SID^+]) + [H^+]^2(K_a([SID^+]) - [A_{TOT}]) - (K'_1 \times S \times pCO_2 + K'_w) \\
- [H^+] (K_a(K'_1 \times S \times pCO_2 + K'_w) + K'_1 \times S \times pCO_2 \times K_3) - K_a \times K_3 \times K'_1 \times S \times pCO_2 = 0.
\end{align*}
\]

where \( K_a \) is the effective equilibrium dissociation constant for weak acids, \( K'_w \) is the ion product of water, \( K'_1 \) is the apparent equilibrium constant for the Henderson–Hasselbalch equation, \( S \) is the solubility of \( CO_2 \) in plasma, and \( K_3 \) is the apparent equilibrium dissociation constant for \( HCO_3^- \).

If this polynomial formula were solved for \([H^+]\), three variables regulate \([H^+]\): SID, \( A_{TOT} \), and \( pCO_2 \). As can be readily appreciated, bicarbonate does not appear in this formula and therefore it is considered to be a dependent variable not directly involved in the regulation of \([H^+]\).

As stated above, SID can be calculated as the difference between strong ions or as sum of bicarbonate and nonbicarbonate buffer base \((A^-)\) (Figure 1). If an abnormal anion is present, a gap will appear between SID calculated by the difference between strong ions (so-called apparent SID or SID\(_a\)) and SID calculated by the addition of bicarbonate and nonbicarbonate buffers (so-called effective SID or SID\(_e\)). This difference, the so-called strong ion gap (SIG), is therefore a marker for the presence of an abnormal anion and is numerically similar to change in the anion gap \((\Delta AG)\) (Figure 1).

### Relevance of Stewart’s Method in Analyzing Acid-Base Disorders

To better understand the relevance of Stewart’s method in analyzing acid-base disorders, I raise and respond to several key questions.

**Is Stewart’s Method Fundamentally Different than the Traditional Method?**

As stated above, proponents of Stewart’s method consider it to be quantitative rather than qualitative and mechanistic rather than descriptive. In reality, Stewart’s method is mathematically a variant of the traditional method [for a full discussion, see the article by Matousek et al. (4)]. Constable, a strong proponent of Stewart’s method, simplified Stewart’s equation by deriving the following equation (5):

\[
\text{pH} = pK'_1 + \log \left( \frac{[SID] - K_a[A_{TOT}]}{(K_a + 10^{-pH})} \right) \times S \times pCO_2
\]

as

\[
(K_a[A_{TOT}])/(K_a + 10^{-pH}) = [A^-].
\]

Schück and Matousovic et al. (6) further simplified the formula as follows:
pH = \text{pK}_1 + \log[\text{SID}] - [A^-]/S \times pCO_2.

As indicated above, \text{SID} = HCO_3^- + A^- and therefore \text{SID} - A^- = HCO_3^-, making the above modified formula very similar to the Henderson–Hasselbalch formula. More recently, Matousek et al. conducted a detailed analysis of the mathematical relationship between these two approaches and found them to be interchangeable (4).

The claim that Stewart’s approach is mechanistic in nature is outside the scope of this editorial; suffice it to say that mathematical proof is not the same as mechanistic proof, with the latter requiring empirical support. There is no empirical proof at this time that \text{SID} directly regulates H^+ concentration [for fuller discussion, readers are referred to Kurtz et al. (7)].

What Is the Clinical Utility of Stewart’s Method? Classification of Acid-Base Disorders. The traditional method is based on robust empirical data developed over the past century in both human as well as animal models. On the basis of these empirical observations, acid-base disorders are classified into six primary disorders: metabolic acidosis (AG and hyperchloremic) and alkalosis, and acute and chronic respiratory acidosis and alkalosis. The compensatory response is now well defined for each disturbance, allowing diagnosis of mixed disturbances. In Table 1, modified from Fencl and colleagues (8), I have matched, as much as possible, each category based on Stewart’s method with the traditional method. A review of this table clarifies several points. First, because pCO_2 is an independent variable, Stewart’s classification of the four primary respiratory acid-base disorders is similar to the traditional method. Second, the major point of disagreement is therefore in the classification of metabolic disturbances, primarily metabolic acidosis. Stewart’s method classifies metabolic disorders based on alteration in the other two “independent variables”: \text{SID} and \text{TA}^- . Although it is easy to match diagnostic categories under “imbalance of strong anion,” other categories deserve further comments (Table 1). Under abnormal \text{SID}, one diagnostic category is “water excess/deficit” characterized by low/high \text{SID} and low/high sodium, respectively. In reality, sodium concentration is primarily regulated independent of acid base; therefore, patients with abnormal serum sodium concentration present with or without acid-base disorders. For example, syndrome of inappropriate antidiuretic hormone secretion, characterized by “water excess” and hyponatremia, is not associated with metabolic acidosis and serum sodium is not elevated in the majority of patients with contraction alkalosis. However, one could argue that water excess/deficit could result in dilutional acidosis and contraction alkalosis, respectively, under very unique circumstances. This lack of clear similarity is indicated with a question mark in Table 1. The next problematic category is acid-base disturbances due to “nonvolatile weak acids,” specifically albumin and phosphate. This is based on the mathematical formula that \text{SID} = HCO_3^- + \text{TA}^- ; therefore, if \text{SID} is unchanged, a decrease in \text{TA}^- must be balanced by an increase in bicarbonate (and therefore metabolic alkalosis) and an

### Table 1. Classification of acid-base disorders using Stewart’s method versus the traditional method

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Acidosis</th>
<th>Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stewart</td>
<td>Traditional</td>
</tr>
<tr>
<td>I. Respiratory</td>
<td>↑ pCO_2</td>
<td>↑ pCO_2</td>
</tr>
<tr>
<td>II. Nonrespiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Abnormal SID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Imbalance of strong anions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Cl excess/deficit</td>
<td>↓ SID, ↑ [Cl]</td>
<td>HCMA</td>
</tr>
<tr>
<td>ii. Unidentified anion excess</td>
<td>↓ SID, ↑ [XA]</td>
<td>AGMA</td>
</tr>
<tr>
<td>2. Nonvolatile weak acids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\text{SID}, \text{strong} \text{ion} \text{difference}; \text{HCMA}, \text{hyperchloremic} \text{metabolic acidosis}; \text{HCMAlk}, \text{hyponchloremic} \text{metabolic} \text{alkalosis}; \text{XA}, \text{unknown} \text{anion}; \text{AGMA}, \text{anion} \text{gap} \text{metabolic} \text{acidosis}; n/a, not applicable. Please see text for explanation. Modified from Fencl V, Jabor A, Kazda A, Figge J: Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 162: 2246–2251, 2000.
increase in TA$^-$ must be balanced with a decrease in bicarbonate (and therefore metabolic acidosis). This is again a mathematical concept that requires empiric proof. McAuliffe et al. reported eight patients with hypoalbuminemia and metabolic alkalosis and calculated that each gram-per-decaliter decrease in serum albumin was associated with a 3.4 mEq/L increase in standard bicarbonate (9). It is, however, important to note that these patients were all hospitalized with severe illnesses, including cirrhosis, burns, SLE, and cancer. Metabolic alkalosis in these patients is often multifactorial and could reflect low effective circulating volume rather than a direct effect of albumin on [H$^+$]. In a study of 935 intensive care unit (ICU) patients, many with low serum albumin, this diagnosis was suspected in only 1 patient (10). Similarly, no study has shown a direct effect of serum phosphate concentration on [H$^+$].

**Does Stewart’s Method Diagnoses Hidden Acid-Base Disorders Missed by the Traditional Method?**. Proponents of Stewart’s method would respond affirmatively to this question. This response is based on the concept that Stewart’s method, by using SID and SIG, provides a more detailed assessment of acid-base disorders. It is argued that if SID is calculated by using all cations and anions, it achieves a higher level of accuracy than the AG calculated by using the standard calculation. Proponents of the traditional method would argue that AG could also be calculated by including all measurable cations and anions. In addition, because SIG is calculated as the difference between SID$_a$ and SID$_e$ and $\Delta$AG as the difference between abnormal and normal AG, the effect of minor cations and anions, for all practical purposes, is cancelled (Figure 1) (11). This is supported by the empirical observation in a large group of patients that numerical values for SIG and $\Delta$AG, as expected, are nearly similar (12). However, the traditional approach is criticized appropriately for ignoring TA$^-$, which is contained in SID (13). The traditional method has accepted this deficiency by correcting AG for changes in serum albumin, the major component of TA$^-$.

Many studies have compared the utility of SIG versus corrected AG (AG$_C$) and found that it was no more accurate in making a diagnosis. For example, Fencl et al. in a study of 152 ICU patients, 96% of whom had severe hypoalbuminemia, reported that Stewart’s method diagnosed underlying metabolic acidosis in 20 patients with normal BE and 22 patients with normal bicarbonate. However, when AG was corrected for hypoalbuminemia, it was elevated in all of the samples with normal [HCO$_3^-$], making the diagnosis of hidden metabolic acid-base disorders possible (8). In a prospective observational study of 935 ICU patients, Dubin et al. found that Stewart’s method detected metabolic disorders in 131 patients (14%) with normal bicarbonate and BE, whereas the traditional method made a similar diagnosis in 108 patients (13%). Stewart’s method, however, failed to make an important acid-base diagnosis in 27 patients (3%) compared with the traditional method using AG$_C$ (10). Two recent studies in patients with septic shock and liver transplantation again confirmed very tight correlation between SIG and AG$_C$ (14,15). Interestingly, using a simplified calculation of SID, SID = ([Na] – [Cl]), Mallat et al. found a very strong relationship between SIG and AG$_C$ ($r=0.98$) (16). In summary, if AG$_C$ is used in analysis of acid-base disorders, the traditional method performs as well or better than Stewart’s method (11).

**Does Stewart’s Method Provide a More Accurate Prognosis than the Traditional Method?**. Although the major goal of any proposed method is primarily to provide accurate diagnosis critical to initiating appropriate therapy, many recent studies have attempted to evaluate the prognostic ability of these two approaches. These studies were extensively discussed previously (11) and are summarized as follows: (1) correction of AG by serum albumin level increases its predictive power; (2) AG$_C$ performs as well as SIG in predicting mortality; (3) although the receiver operating curve for SIG and AG$_C$ achieves clinically useful significance in two studies, reported receiver operating curves were too low to be of clinical use in other studies; and (4) SIG should be more appropriately compared to $\Delta$AG rather than AG$_C$ (see above). This has not been done.

Although these studies are interesting, they have little clinical utility in managing these patients who often are acutely ill with multiple comorbidities. Several studies have shown that clinical assessment tools such as the Injury Severity Index, Pediatric Index Mortality, and the Acute Physiology, Age, Chronic Health Evaluation are as or more powerful than specific laboratory assessments. In reality, the clinical outcome in these patients depends on many independent clinical and laboratory variables, which may or may not include acid-base parameters.
Stewart, using sound physical principals, has proposed a new approach to the diagnosis of acid-base disorders. However, Stewart’s method is not new and is both mathematically and biochemically a variation on the traditional method. It also fails to provide a more mechanistic and quantitative view of acid-base disorders than the traditional method. However, Stewart’s approach has opened a different window to these complex disorders and as such has clarified the role of TA− and the importance of correcting AG for changes in serum albumin. Clinically, however, this approach is not intuitive and requires relatively complex calculations. Although this approach is intellectually interesting, it does not outperform the traditional approach at the bedside. Despite this, it is important that nephrologists appreciate Stewart’s contributions and become familiar with this approach, which has gained increasing acceptability among anesthesiologists and intensivists.

Disclosures
None.

References
Syllabus
Fluid, Electrolyte, and Acid-Base Disturbances

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Learning Objectives
1. To examine recent scientific advances in our understanding of the pathophysiology of disorders of potassium, acid-base, sodium, and water balance
2. To review how our understanding of pathophysiology can be applied to the care of patients
3. To analyze how recent clinical trials related to fluid, electrolyte and acid-base disorders can be applied to clinical decision making

This NephSAP issue devoted to fluid and electrolyte disorders is taking the form of a case-based approach to interesting clinical topics. It is more in the form of a primer as has been the case with some special issues such as the NephSAP on renal pathology. This does not represent a philosophical change for NephSAP but rather results from the observation that although fluid and electrolyte problems continue to be a major focus for the nephrology community, there is a relative dearth of clinical trials or extensive observational studies in this arena since the last update. In addition, the use of case-based teaching methods has been requested by NephSAP readers and previous examples of this approach received high marks from reviewers. The accompanying examination, although derived from many of the cases, is also broader in scope than typical examinations, reflecting the broader focus of the syllabus.

Case 1: Hyperkalemia

A 75-year-old man with a 9-year history of chronic lymphocytic leukemia is evaluated for severe fatigue and anorexia. Past medical history is significant for diabetes mellitus, hypertension, well compensated heart failure, and a colonic fistula due to diverticulitis 3 years previously. Medications include an oral hypoglycemic agent, a β blocker, an angiotensin converting enzyme (ACE) inhibitor, and an angiotensin receptor blocker (ARB).

An outpatient bone marrow biopsy shows morphologic changes indicating transformation to diffuse large-cell non-Hodgkin’s lymphoma and his peripheral blood smear indicates leukemic blast crisis. He is admitted to begin chemotherapy.

The patient’s physical examination on admission is unremarkable except for a heart rate of 56 beats per minute. His laboratory data on admission reveal the following: hemoglobin, 7.6 g/dl; white blood cell count, 479,000 with 95% lymphocytes and 5% blasts; platelets, 17,000; serum potassium, 9.8 mEq/L (nonhemolyzed specimen); uric acid, 11.8 mg/dl; serum creatinine, 1.5 mg/dl (estimated GFR 40 ml/min per 1.73 m²); and lactate dehydrogenase, 2529 IU/L.

A repeat blood sample is collected while obtaining an urgent electrocardiogram (EKG). The EKG shows sinus bradycardia with a normal QRS interval and no peaking of the T waves, but the repeated potassium result is 9 mEq/L.

Which ONE of the following statements is true?
A. Because the platelet count is low and there is no hemolysis, pseudohyperkalemia need not be considered.
B. The patient has hyperkalemia from tumor lysis syndrome and should be treated immediately with intravenous calcium chloride, glucose, and insulin,
and oral sodium polystyrene sulfonate (SPS) (kayexalate).

C. Although dual therapy with an ACE and ARB decreases all cause mortality in patients with hypertension and diabetes, he should not have been treated with this combination because of a high incidence of hyperkalemia when the GFR is $<60 \text{ ml/min per } 1.73 \text{ m}^2$.

D. Chronic low-dose SPS has been used successfully to control hyperkalemia in patients with hyperkalemia and CKD treated with ACE and ARB.

Discussion

The correct answer is D. Although the patient is at increased risk of developing hyperkalemia because of diabetes, CKD, suppression of the renin-angiotensin system (RAS), and possible tumor lysis, pseudohyperkalemia should be strongly suspected because of the patient’s hematologic disorder, the normal EKG, and the absence of symptoms despite extreme hyperkalemia. Careful separation of the serum revealed this to be the case (1) (Figure 1-1).

If the patient did have true hyperkalemia due to tumor lysis, administration of intravenous calcium would not be indicated in the absence of advanced electrocardiographic changes, and might be harmful because tumor lysis is often accompanied by hyperphosphatemia (2,3). SPS is of dubious benefit in the emergency management of severe hyperkalemia (4). Dual therapy with ACE and ARB has not been shown to have a survival benefit, but it does modestly increase the risk of hyperkalemia (5). Low-dose SPS has been successfully used chronically in patients with CKD treated with inhibitors of the renin-angiotensin-aldosterone system (RAAS) (6). However, this agent is not ideal because of the potential of bowel injury (a serious concern in this patient given his past history) (7) and new experimental agents on the horizon will hopefully provide us with safer and more effective options (8).

Pseudohyperkalemia

Spurious hyperkalemia, or pseudohyperkalemia, should be considered in any patient with marked leukocytosis or thrombocytosis. Early recognition of spurious potassium values can avoid potentially harmful interventions.

Because potassium is released from platelet granules during coagulation, comparison of the potassium concentration of serum (separated after centrifugation of

a clotted blood specimen) and plasma (obtained by centrifugation of heparinized blood) or whole blood potassium (measured by potentiometry in a sample obtained in a blood gas syringe) will identify pseudohyperkalemia in patients with thrombocytosis (9–12). In contrast to thrombocytosis, which elevates the serum potassium but not the plasma potassium, marked leukocytosis can falsely elevate the potassium concentration of both serum and plasma because of leakage of potassium from leukemic cells during standing or after white cell lysis during phlebotomy using vacuum tubes or transport of blood samples in pneumatic tubes (13,14); in patients with leukemia, the plasma concentration may be higher than the serum potassium—a phenomenon that has been called reverse pseudohyperkalemia (15–17). Heparin-induced damage to the cell membrane of leukemic cells has been postulated to be the cause of reverse pseudohyperkalemia. Tubes used for collecting peripheral blood contain three times as much heparin as a blood gas syringe used to determine whole blood potassium. Therefore, if reverse pseudohyperkalemia is suspected, a whole blood specimen collected in a balanced heparin syringe should be analyzed on the blood gas analyzer; a promptly processed serum potassium determination may also be helpful.

Several genetic defects can cause pseudohyperkalemia by causing abnormal leakage of potassium from red cells; missense mutations may generate cation leak pathways through the mutant proteins themselves or by deregulating one or more independent cation permeabilities of the red cell membrane (18). Recently, two mutations in residue 375 of the ABCC6 transporter have been identified that are the cause of familial pseudohyperkalemia, a dominant red cell trait characterized by increased serum potassium concentrations measured in whole blood specimens stored at or below room temperature. This dominantly inherited trait is not accompanied by clinical symptoms or biologic signs except for borderline abnormalities of red cell shape. Familial pseudohyperkalemia is considered as a subtype of the larger group of leaky red blood cell disorders that include Southeast Asian ovalocytosis and hereditary stomatocytosis. An unusual inherited variant of GLUT1 deficiency was recently described characterized by hyperkalemia, neonatal hyperbilirubinemia, hemolytic anemia, hepatic dysfunction, microcephaly, seizures, developmental delay, periventricular calcification, cataracts, and retinal dysfunction. Extremely leaky red cells in the condition are the cause of hemolysis and temperature-dependent loss of potassium from red cells causing both hyperkalemia and pseudohyperkalemia (19).

Handling of specimens from people without hematologic or genetic abnormalities can also result in pseudohyperkalemia. A study comparing potassium results from samples obtained in off-site phlebotomy centers to those obtained from an on-site draw center found a significantly higher percentage of values above the reference range (20). Patient samples for potassium and chemistry profiles were routinely collected in heparinized plasma separator tubes, centrifuged, and transported by courier from the off-site center to a central laboratory within several hours, whereas specimens from the on-site phlebotomy were similarly collected but sent uncentrifuged to the central laboratory via a pneumatic tube system within several minutes after collection. The off-site samples were subjected to various degrees of jostling, which could potentially contribute to false elevation of $K^+$ due to cell lysis during transportation. In addition, it was found that during transport there was “red blood cell escape” through the inert gel barrier of the collection tube into the separated plasma. The laboratory solved the problem by changing to serum samples at off-sites, and centrifuging and separating the serum before transport. Spurious hyperkalemia is particularly relevant in laboratories serving large geographic areas where sample transport can cause significant delays in sample centrifugation. A study in rural Scotland found that the introduction of centrifuges at practice sites significantly reduced the number of cases of spurious hyperkalemia and diminished the effect of seasonal variation in serum potassium results (21).

**Electrocardiographic Findings in Hyperkalemia**

The absence of EKG findings of and symptoms of hyperkalemia were a clue to the diagnosis of pseudohyperkalemia in this patient. Potassium levels of 9 mEq/L are almost invariably associated with dramatic EKG findings and severe muscle weakness (22–26). Tolerance to hyperkalemia varies considerably between individuals; approximately 50% of patients have EKG changes at a serum potassium $>6.5$ mEq/L (27). Green and coworkers correlated 12-lead EKGs and serum potassium measurements in 145 patients with ESRD and found that tenting of T waves was as common in normokalemia as it was in
hyperkalemia. The investigators found that a ratio of the T wave to the R wave (T:R) $\geq 0.75$ was more specific than tenting (67% versus 85%) in detecting a serum potassium $\geq 6.0$ mEq/L but neither test was very sensitive (33% versus 24%) (28). Mohanlal et al. described three cases of profound bradycardia without other findings of hyperkalemia in three patients with ESRD; after bradycardia failed to respond to atropine, urgent hemodialysis corrected the arrhythmia (29).

**Risk of Hyperkalemia from Renin-Angiotensin Blockade**

Although the patient described in the case vignette above proved to have pseudohyperkalemia, decreased potassium clearance caused by blockade of the RAAS was a plausible cause. Such therapy has been reported to cause extreme life-threatening hyperkalemia in elderly patients with impaired kidney function (30).

Evidence from experimental models showing a synergistic effect between ACE inhibitors and ARBs gave rise to the idea of therapeutic dual blockade of the RAS. Improvement in surrogate endpoints such as BP, proteinuria, and endothelial dysfunction supported the logical conclusion that dual blockade had both cardioprotective and nephroprotective effects. Despite the absence of solid evidence that the regimen is safe and effective, dual therapy has been mentioned in several guidelines for the treatment of hypertension in patients with diabetes or proteinuria or both (5,31).

By the end of the first decade of the 21st century, an estimated 200,000 patients were being treated in the United States with combinations of an ARB and ACE inhibitor (75%), two ACE inhibitors (15%), two ARBs (5%), and ACE inhibitors or ARBs in combination with a direct renin inhibitor (8%).

In a meta-analysis of 33 randomized controls meeting selection criteria, Makani and coworkers compared the long-term efficacy and adverse event profile of dual blockade of the RAS with monotherapy. A combination of an ACE inhibitor and ARB was used in 22 controlled trials, an ACE inhibitor and aliskiren in 3 trials, an ARB and aliskiren in 7 trials, and an ACE inhibitor or ARB with aliskiren in 1 trial.

Mortality was 15.3% in the dual therapy group compared with 15.0% in the monotherapy group. In six trials, 2812 of 19,127 patients (14.7%) died of cardiovascular causes in the dual therapy group compared with 5128 of 326,387 patients (15.7%). Dual therapy had no significant benefit on cardiovascular mortality (relative risk 0.96; 0.88 to 1.05; $P=0.38$) and in subgroup analysis, dual therapy had no benefit on cardiovascular mortality in patients with or without heart failure. There was, however, an 18% reduction in hospital admissions for heart failure ($P=0.0001$), with a trend toward benefit in the cohort without heart failure ($P=0.07$). However, the benefit in hospital admissions for heart failure was offset by a 55% increase in the risk of hyperkalemia (serum potassium $> 5.5$ mEq/L) in the dual therapy group (9.6% versus 4.9%; $P<0.001$) compared with the monotherapy group, in patients with and without heart failure. In addition to an increased risk of hyperkalemia, dual therapy was associated with significantly higher rates of hypotension and kidney failure (serum creatinine $> 2$ mg/dl or doubling of the serum creatinine level).

Similarly, the combination of ARBs and aliskiren significantly increased the risk of hyperkalemia compared with ARBs alone but there was no difference in the risk of other adverse events (5,7).

A meta-analysis by Susantitaphong and coworkers of 59 randomized controlled trials (25 crossover and 34 parallel-arm) comparing the efficacy and safety of combined versus single RAAS blockade therapy in 4975 patients with CKD came to similar conclusions (32).

**Sodium Polystyrene Sulfonate for Hyperkalemia**

In a retrospective study, Chernin and coworkers analyzed the efficacy and safety of daily administration of 15 g of sorbitol-free sodium polystyrene sulfonate in 14 patients with CKD and heart disease who developed hyperkalemia while treated with ACE, ARB, and/or spironolactone (6). The mean serum potassium fell from $6.4 \pm 0.3$ mEq/L (range, 6.0–7.1 mEq/L) to $4.5 \pm 0.6$ mEq/L (range, 3.0–5.8 mEq/L) ($P<0.01$). Mild asymptomatic hypokalemia (3.1 and 3.0 mEq/L) developed in two patients who were managed with a dose reduction to alternate-day therapy. The drug was well tolerated without severe adverse events.

Despite a black-box warning by the US Food and Drug Administration that the combination of sorbitol and sodium polystyrene sulfonate can be associated with bowel necrosis, the combination continues to be widely prescribed for both acute and chronic hyperkalemia (33) and case reports of gastrointestinal injury continue to appear in the recent literature (34,35). Harel and coworkers reviewed the literature and found
30 reports describing 58 cases of gastrointestinal injury (41 preparations containing sorbitol and 17 preparations without sorbitol) (7). Injury to the colon was most common (75%) with transmural necrosis in 62% of cases. Mortality was 33% in the reported cases.

In a retrospective cohort study, Watson and coworkers found 82 cases of inpatient bowel necrosis (0.14%) among 2194 patients treated with oral SPS (1 g of sodium polystyrene in 33% sorbitol); only 3 (0.14%) among 2194 patients treated with oral SPS were similar in a subgroup with concomitant CKD. RLY5016 is a polymer synthesized as a 100-μm bead with optimized flow and viscosity properties and it does not require administration with a cathartic to reach the colon.

Zirconium silicate is another experimental selective potassium binder that is not systemically absorbed. According to the company developing this agent, it appears to be 10 times as potent as SPS in binding potassium (H. Rasmussen, personal communication, March 7, 2013). A phase 2 trial in 90 patients with CKD and mild to moderate hyperkalemia has been completed and a phase 3 trial in a total of 750 patients with hyperkalemia (serum potassium 5.0 to 6.5) was begun in approximately 75 sites in North America, Europe, and Australia.

### References

Case 2: Hyponatremia

A 40-year-old woman with a past history of hepatitis C presents with nausea, right upper quadrant pain, and weakness. Her BP is 120/70 mmHg and her heart rate is 104 beats per minute without orthostasis. Physical examination reveals scleral icterus and liver tenderness without ascites or peripheral edema. Her mental status is normal and she has no asterixis.

Her laboratory data are as follows: serum Na, 118; serum K, 3.5; serum Cl, 89; CO2, 25 mmol/L; BUN, 4; blood glucose, 80 mg/dl. Her plasma osmolality is 297 mOsm/kg. In addition, her other serum results are as follows: protein, 4.9 g/dl; albumin, 1.9 g/dl; total bilirubin, 14.1 mg/dl; alkaline phosphatase, 1524 U/L; aspartate aminotransferase, 136 U/L; and alanine aminotransferase, 82 U/L. The serum is nonlipemic and serum triglycerides, thyroid function tests, and cortisol levels are within normal limits.

A liver biopsy shows portal mixed inflammatory edema with bile ductal proliferation and hepatocellular cholestasis—changes that are consistent with a biliary obstructive process with mild iron pigment deposition in the Kupffer cells and moderate portal fibrosis.
B. The absence of lipemic serum and the normal serum proteins and triglycerides exclude the possibility of pseudohyponatremia.

C. If the serum sodium were measured by a laboratory autoanalyzer utilizing an ion-specific electrode, pseudohyponatremia could be excluded.

D. Additional testing is needed to interpret the serum sodium concentration.

Discussion

The correct answer is D. Additional testing showed cholesterol of 2621 mg/dl, with LDL cholesterol of 1786 mg/dl, apoB100 of 177 mg/dl, and lipoprotein A of 100 mg/dl, suggesting that the elevated level of LDL cholesterol was due to lipoprotein X accumulation secondary to inadequate bile excretion. Measurement of the serum sodium with direct potentiometry confirmed that the patient had pseudohyponatremia (Figure 2-1) (1).

The patient described here has severe liver disease, which is often associated with hyponatremia. However, the measured plasma osmolality (297 mOsm/kg) was much higher than what would be calculated (twice the measured serum sodium plus the osmotic contribution of glucose and urea):

\[ 2 \times 118 + 4/2.8 + 80/18 = 241 \text{ mOsm/kg} \]

There are two possible explanations for this finding: pseudohyponatremia or the ingestion of an exogenous solute (ethanol, isopropyl alcohol, methanol, or ethylene glycol). We will discuss these two possibilities as well as the implications of true hyponatremia in the setting of liver disease.

Pseudohyponatremia

A measurement artifact causing a discrepancy between the measured serum sodium and the true sodium concentration in plasma water is called pseudohyponatremia; the same artifact masking true hypernatremia has been called pseudonormonatremia (1,2).

Normal serum is composed of 7% nonaqueous and 93% water portions. Hyperlipidemia and hyperproteinemia increase the nonaqueous portion and decrease the amount of water in a sample of serum. Because sodium is confined to the water phase, the sodium concentration of the whole sample, which includes both aqueous and nonaqueous components, is measured as low.

Most laboratories in the United States use methods that are susceptible to artifactual measurements of the serum sodium concentration. The same artifact affects measurement of potassium, calcium, and chloride; however, although the relative effect on the concentration of these aqueous solutes is identical to that of sodium, the absolute change in the serum sodium concentration is much greater because of its higher concentration in serum.

Serum sodium levels are usually measured with ion-selective electrodes, devices that respond to the activity of an ion rather than its concentration. A sodium-selective membrane immersed into blood or serum determines the sodium activity as a function of the potential difference across the membrane. Although the thermodynamic definition of ionic activity assumes complete ionization under conditions of infinite dilution, for clinical purposes ion activity can be considered to be essentially equivalent to ion concentration.

Because ion-specific electrodes measure the sodium activity in serum water, a value that is independent of the nonaqueous component of the serum sample, the measured value is typically converted to a concentration in total serum (which includes both aqueous and nonaqueous fractions), based on the assumption that 93% of the total sample consists of water. For example, if the sodium concentration is measured by the electrode as
150 mEq in 1 L of serum water, the value will be reported as 139.5 mEq in 1 L of total serum (150 × 0.93 = 139.5).

Although most laboratory autoanalyzers measure the serum sodium with ion-specific electrodes, these instruments are designed to rapidly test a large number of samples, and they require a preanalytical serum dilution step to minimize the amount of serum that is needed; measurement of the serum sodium concentration by this method is called indirect potentiometry. With indirect potentiometry, the result is corrected for the degree of sample dilution based on the assumption that the tested sample was composed of 93% water. Therefore, serum sodium determinations using indirect potentiometry will be spuriously low if the true serum water content is <93%. Blood gas machines can be used to measure the serum sodium concentration without a dilution step; measurement of the serum sodium concentration by this method is called direct potentiometry. The basic principle is the same for both indirect and direct potentiometry, but with severe hyperlipidemia or hyperproteinemia, the indirect method provides inaccurate results (1–4).

In serum containing high concentrations of lipid or protein, the absolute amount of sodium in a given sample volume is decreased; therefore, any dilution by a fixed amount will introduce a dilution error, which decreases the measured serum sodium concentration. Measurement of the serum sodium by direct potentiometry using a blood gas machine avoids the dilution step and prevents the error.

The following equations have been developed to estimate the percentage of water in a serum sample containing high concentrations of lipid or protein:

\[
\% \text{ Serum Water} = 99.1 - (0.0001 \times \text{Lipid concentration in mg/dl}) - (0.7 \times \text{Protein concentration in g/dl})
\]

or in SI units

\[
\% \text{ Serum Water} = 99.1 - (1.1 \times 10^{-5} \times \text{Lipid concentration in mmol/L}) - (0.07 \times \text{Protein concentration in g/L})
\]

The corrected serum sodium value is then calculated by multiplying the indirectly measured serum sodium value by the ratio of the water fraction in normal serum (93%) and the estimated water fraction. For example, if indirect potentiometry of a lipemic sample yields a sodium value of 125 mEq/L and the estimated water fraction is 85%, the corrected serum sodium concentration would be 125 × 93 / 85 = 137 mEq/L.

However, direct gravimetric determinations of the water fraction have shown that the equations used to estimate the water fraction are inaccurate. More complex methods based on chloride levels in serum and its ultrafiltrate or on measurements of serum osmolality before and after dilution have been proposed.

If pseudohyponatremia is suspected, the most practical strategy is to retest the sample using a blood gas analyzer. Direct potentiometry is indicated in the following circumstances: overtly lipemic samples, discrepancy between measured osmolality and calculated osmolality, and severe hypercholesterolemia associated with jaundice.

**Pseudohyponatremia and Hypercholesterolemia Due to Lipoprotein X**

It is a common misconception that pseudohyponatremia can be excluded in patients with hyperlipidemia if the serum is not visibly lipemic. Although severe hypertriglyceridemia can be expected to cause visible turbidity or lipemia of the blood, this is not seen in hypercholesterolemia. Pseudohyponatremia has been reported in hypercholesterolemic patients with obstructive jaundice, associated with increased levels of lipoprotein X (1,5).

Reflux of bile lipoproteins into the bloodstream is thought to be the cause of increased levels of lipoprotein X. If bile lipoproteins are incubated *in vitro* with serum or albumin, lipoprotein X–like particles appear. In patients with severe obstructive or cholesstatic jaundice, lipoprotein X levels can reach several thousand milligrams per deciliter, causing pseudohyponatremia by displacing plasma water. In addition, high concentrations of lipoprotein X increase plasma viscosity, which by reducing the volume of serum aspirated during sample dilution is another mechanism for spurious hyponatremia. Lipoprotein X may cause hyperviscosity syndrome requiring treatment with lipid pheresis. Hyperviscosity can be suspected by the finding of dilated, segmented, and tortuous retinal veins, with a “sausage-link” appearance on funduscopic examination.
**Osmotic Gap Caused by Alcohol Ingestion**

Ingestion of methanol and ethylene glycol causes significant morbidity and mortality if left untreated (6). In addition to causing high anion gap metabolic acidosis, methanol is metabolized to formic acid, which causes ocular toxicity, and ethylene glycol is metabolized to oxalic acid, which causes permanent kidney injury. Therapy with alcohol dehydrogenase inhibitors, such as fomepizole or ethanol, or hemodialysis can prevent further end organ damage. However, before embarking on these potentially harmful and expensive interventions, confirmation of toxic alcohol ingestion is desirable. Unfortunately, most clinical laboratories are unable to measure these alcohols directly. To avoid therapeutic delays, the osmolar gap has long been used as a surrogate to identify toxic alcohol ingestion (7–10).

In an ideal solution, the contribution of a solute to plasma osmolarity is in direct proportion to the solute’s molar concentration. On the basis of this premise, plasma osmolarity can be estimated by adding the concentrations of the most prevalent solutes: sodium and its corresponding anions as well as glucose and urea. If glucose and BUN concentrations are reported in milligrams per deciliter, the most commonly used equation for calculating osmolarity is as follows:

\[
\text{Plasma osmolality} = 2 \times [\text{Na}^+] + (\text{Glu} / 18) + (\text{BUN} / 2.8)
\]

If glucose and urea concentrations are reported in mmol/L, the equation is simply:

\[
\text{Plasma osmolality} = 2 \times [\text{Na}^+] + \text{Glu} + \text{BUN}
\]

Because there are inaccuracies inherent in this popular formula, others have been proposed. Sodium salts do not completely dissociate in plasma, leading to the suggestion that the coefficient in the first term should be approximately 1.86 rather than 2. Because other solutes are normally present in plasma, the estimated osmolality differs from the measured value, creating a normal “osmolar gap” of 5–10 mOsm/L; therefore, some osmolality estimates include that factor in the calculation. However, one study showed that the normal osmolar gap can range from −14 to 10.

When the osmolar gap is too high, this suggests that a solute other than glucose or urea is present in a high enough concentration to significantly raise the plasma osmolarity. Potential culprits include alcohols, the osmotic diuretics mannitol and sorbitol, glycine and sorbitol absorbed during surgical procedures, and sucrose and maltose contained in Ig preparations. Among these, ethanol is by far the most common.

Ethanol has a molecular weight of 46 and is infinitely soluble in water. Theoretically, each milligram of ethanol per deciliter of plasma should contribute approximately 0.22 mOsm/kg to plasma osmolality (i.e., the contribution to plasma osmolality is calculated by dividing the ethanol level, in milligrams per deciliter, by 4.6). However, some investigators have found that when ethanol levels are high, commonly used conversion factors produce an inaccurate estimate of plasma osmolality; the slope of a regression of the osmolar gap against plasma ethanol levels is >0.22 (the actual osmolar contribution of ethanol exceeds what would be predicted from its concentration in plasma). A regression of samples taken from 603 patients had a slope of 0.25, so that the best fit equation to predict the change in osmolar gap per unit of ethanol concentration was as follows:

\[
\Delta \text{Osmolar gap}(\text{mOsm/L}) = \text{Ethanol}(\text{mg/dl}) / 4.0.
\]

The reason why ethanol contributes more to the plasma osmolarity than expected from its concentration in plasma is unknown, but the authors suggest that it may be related to ethanol partitioning between aqueous and nonaqueous phases in plasma. The addition of pure ethanol to plasma in the test tube produced a coefficient that also differed from the predicted value, perhaps due to the same postulated partitioning phenomenon.

The osmolar gap is not a reliable test to identify toxic alcohol ingestion because it is influenced by many disease states, toxins, and medications, including sepsis, lactic acidosis, and ketosis (Figure 2-2) (6–8, 10–12). Osmolar gaps >50 mOsm/L are most likely the result of alcohols because very few medical conditions or drugs can elevate a gap to that extent. However, it should be recognized that the osmolar gap is an inherently imprecise estimate and is subject to large errors and that the contribution of ethanol is one of these.

**Other Causes of an Osmolar Gap**

In addition to pseudohyponatremia from increased concentrations of lipids and proteins, the
presence of an osmolar gap can help in the evaluation of nonhypotonic hyponatremia caused by the administration of mannitol or immune globulin containing sucrose or maltose or by the absorption of glycine, sorbitol, or mannitol irrigants during endoscopic surgery. A high osmolar gap has also been reported to be predictive of contrast-induced AKI (13).

Hyponatremia in Cirrhosis

The Cirrhotic Ascites Patient Population Survey (CAPPS) researchers collected data from 28 centers on 997 patients with liver disease cared for by hepatologists. Hyponatremia was found in 57% of inpatients and 40% of outpatients, including serum sodium levels ≤ 135 mEq/L in 49.4%, ≤ 130 mEq/L in 21.6%, ≤ 125 mEq/L in 5.7%, and ≤ 120 mEq/L in 1.2% (14). A similar prevalence of hyponatremia has been found in other studies of admitted patients. The CAPPS series found that hyponatremia was associated with severe ascites, large fluid accumulation rate, requirement for frequent large-volume paracentesis, and impaired renal function. A serum sodium ≤ 130 mEq/L was associated with significantly greater risks for hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis. Patients with a serum sodium of 131–135 mEq/L had a greater risk of hepatic encephalopathy and hepatorenal syndrome compared with normonatremic patients.

Serum sodium concentrations ≤ 130 mEq/L are especially common in patients awaiting liver transplant (14–16). Among 213 consecutive patients with cirrhosis undergoing orthotopic liver transplantation at a single center, 42% developed a serum sodium ≤ 130 mEq/L at some point before transplantation, and 16% remained persistently hyponatremic at the time of transplantation. Similarly, data from several transplant databases have consistently shown that approximately 31% of patients waiting for transplant have a serum sodium < 135 mEq/L.

A number of recent studies have shown that hyponatremia is an independent predictor of mortality in patients with ascites due to portal hypertension, and is significantly associated with increased severity of liver disease assessed by Child-Pugh scores and Model for End-Stage Liver Disease (MELD) scores as well as a greater risk of spontaneous bacterial peritonitis and hepatic encephalopathy (14, 16, 17). Hyponatremia is associated with increased mortality in patients on the
liver transplant waiting list, increasing the hazard ratio by 1.05 per 1-unit decrease in serum sodium level from 140 to 125 mEq/L ($P<0.001$).

A new scoring system to adjust the traditional MELD score was developed based on serum sodium (MELD-Na score: $\text{MELD} + 1.59$ (135 – serum sodium) for maximum and minimum sodium concentrations of 135 and 120 mEq/L, respectively). MELD plus hyponatremia ($\leq 130$ mEq/L) predicted mortality significantly better than MELD alone ($P=0.01$). However, the MELD-Na score was based on a population with relatively mild hyponatremia; a single-center study showed that for serum sodium levels $<125$ mEq/L, the serum sodium concentration itself or the Child-Pugh score was a better predictor of mortality than the MELD-Na score (17).

It has been suggested that low-grade cerebral edema associated with hyponatremia may predispose cirrhotic patients to encephalopathy by exacerbating astrocyte swelling caused by ammonia (16). Hyperammonemia increases intracellular glutamine in astrocytes via the glutamine synthase pathway, raising intracellular osmolality and promoting fluid movement into cells. However, glutamine accumulation in astrocytes is not temporally correlated with the extent of cell swelling. Recently, another mechanism, known as the Trojan horse hypothesis, postulates that glutamine is transported into mitochondria, where it undergoes hydrolysis to yield high levels of ammonia, which causes oxidative/nitrative stress (18).

Adaptive mechanisms control brain swelling through extrusion of electrolytes and organic osmoles. These adaptations also make the brain susceptible to injury in response to overly rapid increases in serum sodium (14,16). Patients with severe malnutrition, alcoholism, or advanced liver disease are believed to be more susceptible to osmotic demyelination syndrome after rapid correction of hyponatremia. Large increases in the serum sodium concentration are common in patients undergoing liver transplantation because of the huge volumes of blood products and isotonic fluids that must be given during the procedure.

A study of 512 patients receiving a liver transplant at the Seoul National University Hospital found that patients with serum sodium concentrations $<125$ mEq/L had higher rates of in-hospital mortality, delirium, neurologic complications, and AKI (Figure 2-3) (19). Although serum sodium levels were not associated with neurologic complications, after correcting for the effects of pretransplant hyponatremia in a multivariable analysis, the total increase in serum sodium concentration during the first 48 hours after liver transplantation showed a significant association with post-transplant neurologic complications (new stupor, coma, and tremors, seizures, neuropahty, and focal neurological findings) ($P=0.003$). Fast correction rates during a 24-hour period were also significantly associated with neurologic complications ($\Delta \text{Na}$ $\geq 12$ mEq/L per 24 hours, $P=0.02$; and $\Delta \text{Na}$ $\geq 16$ mEq/L per 24 hours, $P=0.002$). Figure 2-1 shows the association between a rapid rate of correction and neurologic complications based on the severity of hyponatremia divided in quartiles. A rapid rate of correction was defined as the upper 15th percentile of the correction rate for each group ($>16$ mEq/L per 24 hours for a serum Na $\leq 128$ mEq/L; $>11$ mEq/L per 24 hours for Na $128–133$ mEq/L; and $>8$ mEq/L per 24 hours for Na $>133$ mEq/L). The investigators did not find definite cases of central pontine myelinolysis or permanent neurologic sequelae but they did not perform routine magnetic resonance imaging to detect subtle lesions. Another single study from a transplant center in Korea found that a $>10$ mEq/L increase in serum sodium concentration during surgery was associated with prolonged mechanical ventilation ($P=0.01$) (20).

Hyponatremia in patients with cirrhosis and portal hypertension is mediated by arginine vasopressin, which...
is released in response to a reduced effective arterial volume caused by arterial splanchnic vasodilation. Vasopressin receptor antagonists, which inhibit the effects of arginine vasopressin and increase free water excretion, have been evaluated in hyponatremic patients with cirrhosis. Although conivaptan appears to be effective in raising the serum sodium concentration (21), it may not be advisable to use it in patients with cirrhosis because of the possibility that V1A inhibition may result in splanchnic vasodilation, which could predispose to hepatorenal syndrome or variceal bleeding. The selective V2 receptors tolvaptan, lixivaptan, and satavaptan have all been shown to be superior to placebo in decreasing urine osmolality and increasing serum sodium concentrations in patients with cirrhosis, but recent data have raised concerns about their safety. Meta-analyses of three randomized, double-blind phase 3 trials involving 1200 patients with uncomplicated and difficult to treat ascites found that the experimental drug, satavaptan, was no more effective than placebo in preventing hepatic encephalopathy or in controlling ascites over a 1-year treatment period (22–24). More disturbingly, one of the three trials reported a significant increase in mortality with satavaptan versus placebo (29.4% versus 21.7%, respectively; \(P=0.05\)) (23). Given the limited benefit and safety concerns, the manufacturer discontinued development of this agent in 2008.

Tolvaptan is the only selective V2 receptor antagonist that is approved by the US Food and Drug Administration. A subanalysis of the 63 tolvaptan-treated patients and 57 placebo patients with cirrhosis who were enrolled in the randomized, placebo-controlled SALT trial of this agent showed that the proportion of patients who normalized their serum sodium was significantly greater with tolvaptan than placebo at day 4 (41% versus 11%; \(P=0.0002\)) and that mental component summary scores of the Medical Outcomes Study 12-item Short Form General Health Survey improved from baseline to day 30 in the tolvaptan group but not the placebo group (4.68 versus 0.08; \(P=0.02\)) (20,25). However, gastrointestinal bleeding was reported in 6 of 63 tolvaptan-treated patients (10%) and in only 1 of 57 placebo-treated patients (2%) \(P=0.11\). Given the concern for this complication, tolvaptan should be used in cirrhotic patients only when the need to treat outweighs the risk of gastrointestinal bleeding.

One of the most compelling reasons for correcting hyponatremia in patients with cirrhosis is in those awaiting transplantation to avoid an abrupt perioperative increase in serum sodium concentration. Continuous dialysis techniques have been utilized for this purpose (26). O’Leary and Davis described a series of 11 hyponatremic patients prepared for liver transplant with a 2-day infusion of intravenous conivaptan (21). Tolvaptan would be a reasonable strategy as well.

References
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Case 3: Hyponatremia

A 49-year-old woman with no previous medical history competed in the Marathon of Paris on a warm day (27°C). She completed the 42-km run in 5 hours and 30 minutes. During the race, she consumed mineral water (containing 5 mg/L NaCl) and ate several energy bars.

Four hours after finishing the marathon, she felt dizzy, nauseous, and extremely weak, and vomited three times. Subsequently, she became disoriented and confused and was brought to the emergency room 7 hours after her symptoms began.

On admission, she was conscious but disoriented and obtunded, with a Glasgow coma score of 13. Her body weight was 53.4 kg, 3.4 kg above her normal weight. She was afebrile and vital signs were normal. The neurologic examination showed generalized hyperreflexia, but there were no focal findings and plantar reflexes were flexor.

The patient’s laboratory data were as follows: hemoglobin, 10.1 g/dl; white blood cell count, 11,000; platelet count, 172,000; serum Na, 121; serum K, 3.3; serum Cl, 88; serum CO₂, 18 mmol/L; plasma osmolality, 260 mOsm/kg; BUN, 8 mg/dl (2.9 mmol/L); creatinine, 0.8 mg/dl (68 μmol/L); glucose, 153 mg/dl (8.5 mmol/L); uric acid, 3.6 mg/dl (214 mmol/L); lactic acid, 1.2 mmol/L; Ca, 7.2 mg/dl (1.8 mmol/L); phosphorus, 2.7 mg/dl (0.87 mmol/L); Mg, 1.04 mmol/L; total protein, 70 g/L; CPK, 14,486 UI/L; PaO₂, 101 mmHg; SaO₂, 97.8% (ambient air); urine osmolality, 489 mOsm/L; urine Na, 86; and urine K, 75 mmol/L.

Three hours after admission, after treatment with 750 ml of isotonic (0.9%) saline, the patient had a generalized tonic-clonic seizure that resolved after a 1 μg intravenous injection of clonazepam. An additional 2.5 L of isotonic saline was given but repeat laboratory data showed that the serum sodium was still 121 mmol/L. A computed tomography (CT) scan of the brain showed diffuse supratentorial cerebral edema (Figure 3-1 and Table 3-1).

The patient’s neurologic symptoms resolved and she recovered uneventfully, with no neurologic abnormalities at the time of discharge from the hospital.

Which ONE of the following questions about this patient is true?

A. Hyponatremia could have been avoided if the patient had consumed sports drinks rather than mineral water.

![Figure 3-1. Noncontrast computed tomography scan on day of admission. Reprinted with permission from Kormann R, Philippart F, Hubert S, Bruel C: Marathon runner with acute hyponatremia: A neurological disorder. *Case Rep Emerg Med* 2012: 342760, 2012.](image-url)
The laboratory findings and clinical course support a diagnosis of cerebral salt wasting.

The serum sodium increased too rapidly because the dose of hypertonic saline was too large.

Despite a rising serum sodium concentration, vasopressin levels probably fell during the infusion of 3% saline.

Discussion

The correct answer is D. This remarkable case report (1), with additional details as graciously provided by the authors in a personal communication (February 08, 2013), tells us a great deal about acute water intoxication (Figure 3-1). The patient described in the report drank water in excess of water losses so that instead of the 2% decrease in body weight to be expected by consumption of muscle glycogen, her weight increased by 6.8%; weight gain of this magnitude during a marathon is associated with a 45% probability of developing hyponatremic encephalopathy (2). As discussed below, had she consumed sports drinks rather than mineral water, the outcome would not have been different. Her urine sodium on admission was high; her weight gain reflects extracellular volume expansion, consistent with syndrome of inappropriate antidiuretic hormone secretion (SIADH) and not cerebral salt wasting, which will have identical laboratory findings. Exercise-induced hyponatremia is associated with transient inappropriate antidiuretic hormone (ADH) secretion; therefore, aggressive therapy with hypertonic saline is indicated. This patient’s large urine output associated with a greater than expected increase in serum sodium concentration after a modest dose of 3% saline suggests that vasopressin levels fell late in her course, permitting a water diuresis to occur.

Marathons attract scores of nonprofessional runners like the patient described here. Exercise-associated hyponatremia (EAH) is common, and several factors seem to increase the risk, including female sex, low body weight, lack of training, slow running pace (>4 hours for a conventional marathon), excessive consumption of water during the run, use of nonsteroidal anti-inflammatory agents, warm air temperature, and water availability at stations along the race course. The incidence of EAH has been estimated to be as high as 51% in ultramarathon runners, 18% in Ironman triathletes, 16% in hikers, 13% in standard marathon (42 km) runners, and 12% in endurance cyclists (3).

Sports Drinks and EAH

With a sodium concentration <20 mEq/L, sports drinks are mostly electrolyte-free water; if retained, they should be as likely to cause hyponatremia as tap water. Yet, as discussed extensively in a recent BMJ feature and a series of articles in the journal, these drinks are widely believed by the public and by some medical professionals to be protective of this complication in runners (4,5). The feature asserts that the sports drink industry has promoted this belief along with popular myths about hydration and athletic performance that are believed to be responsible for the disturbingly high incidence of water intoxication among amateur competitive runners.

For many years, athletes have been bombarded with information about what they should drink, and when, during exercise. Current drinking dogmas urge runners to prehydrate, drink ahead of thirst, train their intestines to tolerate more fluid, and to know that their brain does not know when they are thirsty. By contrast, in the 1970s, marathon runners were discouraged from drinking fluids for fear that they would slow them down.

The first sports drink, named Gatorade after the football team it was intended to hydrate, was developed in the 1960s by a nephrologist at the University of Florida. The drink contained water, sodium, sugar, and monopotassium phosphate with a dash of lemon flavoring. It was claimed that the new drink could prevent and cure dehydration, heat stroke, and muscle cramps, and improve performance. The increased popularity of road running, which began with the first New York marathon in 1970, provided a burgeoning market for the new product, spawning a billion-dollar industry.

The BMJ feature provides evidence that sports drink companies have sponsored scientists, who

<table>
<thead>
<tr>
<th>Time after 3% NaCl (h)</th>
<th>Serum Na (mEq/L)</th>
<th>0.9% Saline (ml)</th>
<th>3% Saline (ml)</th>
<th>Urine Output (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−11</td>
<td>121</td>
<td>1916</td>
<td>−</td>
<td>?</td>
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<tr>
<td>0</td>
<td>121</td>
<td>1133</td>
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<td>4</td>
<td>128</td>
<td>200</td>
<td>1917</td>
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<tr>
<td>7</td>
<td>136</td>
<td>−</td>
<td>730</td>
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Treatment with 3% NaCl at 50 ml/h was started 8 hours after the seizure and was continued for 4 hours (total infusion of 200 ml).

Table 3-1. Change in serum sodium and urine output

Notes: 3% saline infusion was started 8 hours after the seizure and continued for 4 hours.
proceeded to develop a new area of sports science dedicated to hydration. Sports medicine organizations, advised by these scientists, have developed guidelines that influence health advice by a number of prestigious sources, such as the British Ministry of Defense and the Mayo Clinic’s online guidance to patients, spreading fear about the dangers of dehydration.

Complex algorithms to calculate individual hydration needs have emerged, with advice to rehydrate with a pint for every pound in body weight loss, and to be very concerned about a 2% decrease in weight during exercise. These include instructions on how to calculate sweat rate and to check the color of the urine as a guide to hydration levels. Dark yellow or amber urine has been touted as a sign of dehydration. In 1996, the American College of Sports Medicine produced guidelines that adopted a “zero % dehydration” doctrine, advising athletes to “drink as much as tolerable.” The BMJ feature claims that half of the guideline’s authors had conflicts of interest because of financial ties to Gatorade. The 1996 guidance remained in force until 2007, when an update acknowledged that people should drink according to the dictates of thirst, while still advising that athletes should lose no more than 2% of body weight during exercise.

The public relations effort promoting fear of dehydration was paralleled by the emergence of a new disease: EAH. There were no reports of EAH before 1981 (2,6). Since then, there have been 16 recorded deaths and 1600 people have taken critically ill during competitive marathon running due to hyponatremia. A large National Institutes of Health–funded study found no association with the composition of fluids consumed and concluded that it is the volume of fluid that is the main factor leading to hyponatremia.

Heneghan et al. reviewed 106 studies finding beneficial effects of sports drinks and found serious methodological problems, including small sample size, poor-quality surrogate outcomes, and lack of blinding (7). The BMJ feature cites links between sports medicine journals and their editorial boards and the sports drinks industry as an explanation for the near total absence of negative studies and the difficulty serious investigators face in publishing studies that question the role of hydration.

Causes of Exercise-Induced Hyponatremia

Although the primary explanation for hyponatremia during exercise is excessive water intake, at least three other factors play a role: (1) excessive loss of sodium in sweat, (2) changes in nonosmotically active sodium stores, and (3) inappropriate secretion of ADH and associated urinary sodium losses (8).

Sweat Losses. Ninety-two percent of water losses and 87% of sodium losses during exercise are derived from sweat (9). As in all mammalian secretory systems, sodium and water excretion by sweat glands is a two-step process: first, in response to cholinergic stimulation, the coiled secretory portion of the gland secretes an isotonic primary fluid; and second, sodium and chloride are reabsorbed in the ductal portion of the gland, yielding sweat that is hypotonic to the plasma (10). Differences in electrolyte reabsorption within the sweat duct are responsible for variability in sweat composition among individuals. Activity of the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-activated chloride channel, plays a critical role in transepithelial absorption in the sweat gland, by regulating luminal sodium entry into the ductal cell via the epithelial sodium channel (ENaC).

Loss of CFTR-dependent ENaC conductance affects patients with the inherited autosomal recessive disease, cystic fibrosis, caused by a mutation in CFTR that prevents its insertion in the plasma membrane. Sweat from patients with cystic fibrosis has a 3- to 5-fold higher sodium chloride concentration than sweat from healthy individuals. Some people without cystic fibrosis have sweat sodium levels that approach those found in cystic fibrosis. Two explanations have been offered to explain this finding: (1) healthy individuals with greater salt loss in sweat might be heterozygotes for gene mutations present in cystic fibrosis, and (2) excessive salt losses in sweat might reflect hormonal factors that regulate salt and fluid balance (10).

Brown and coworkers studied the expression of the sweat duct sodium (ENaC) and chloride (CFTR) channels and plasma concentrations of aldosterone and vasopressin before and after exercise in healthy athletes with exceptionally salty sweat, comparing them with patients with cystic fibrosis and with healthy individuals with “typical” sweat sodium composition (10). Genetic testing failed to reveal any of the most frequently occurring mutations in the cystic fibrosis gene in the healthy individuals with salty sweat, but CFTR abundance was decreased in these participants to levels intermediate between normals and patients with cystic fibrosis; ENaC abundance did not differ between the groups.
In addition to differences in expression of CFTR, healthy participants with salty sweat had higher basal plasma arginine vasopressin (AVP) levels but no differences in aquaporin expression in their sweat glands. Aquaporin 5 (AQP5) is expressed in both the secretory coil and distal duct. AVP has been shown to simultaneously decrease sweat rate (possibly by enhancing the water permeability of the secretory coil) and to increase sweat sodium concentrations (possibly by enhancing the water permeability of the duct). However, the role played by aquaporins and AVP in controlling reabsorption at the sweat duct is unknown; therefore, the significance of finding differences in AVP level in the participants remains unclear. Rather than a cause of high sweat sodium, elevated plasma AVP in participants with excessively salty sweat could be an adaptive response to chronic accumulative sweat salt losses during exercise; AVP promotes greater renal conservation of salt by increasing ENaC-mediated sodium transport in renal collecting ducts.

Hew-Butler et al. measured sweat, urine and serum sodium concentrations ([Na⁺]) and plasma concentrations of cytokines, neurohypophyseal and natriuretic peptides, and adrenal steroid hormones in volunteers performing exercise in the laboratory (9). Significant linear correlations were noted between the following: sweat [Na⁺] and postexercise urine [Na⁺] (r=0.80; P<0.001), postexercise serum [Na⁺] versus both postexercise urine [Na⁺] (r=0.56; P<0.05) and sweat [Na⁺] (r=0.64; P<0.01), and postexercise urine [Na⁺] versus postexercise plasma AVP ([AVP] (P)) (r=0.48; P<0.05 (Figures 3-2 and 3-3). These correlations suggest that an increasing serum sodium concentration during exercise evokes an increase in vasopressin concentration that is then responsible for the corresponding changes in sweat and urine [Na⁺] (11).

**Changes in Nonosmotically Active Sodium Stores.** Observational studies of runners have shown that the serum sodium concentration does not fall in all athletes who gain weight during the race (2). This observation has led to the suggestion that mobilization of sodium from nonosmotically active stores in skin or bone might militate against hyponatremia. Runners who develop hyponatremia after modest amounts of water retention might have an impaired ability to mobilize the sodium stores. As discussed in the last fluid and electrolyte volume of NephSAP, Overgaard-Steensen et al. developed a porcine model of acutely decreasing plasma sodium concentration; their data suggested that changes in the serum sodium concentration could be explained by measured sodium, potassium, and water balances with no need to invoke osmotic activation of sodium stores (12). In an interesting letter to the editor, Weschler notes that the equation used to fit the porcine model of acute hyponatremia had different values for the slope and intercept than Edelman’s equation, which was derived from chronic hyponatremia in humans (13). Given the physiologic similarities between the pig and humans, he suggested that these differences might
reflect differences between acute and chronic hyponatremia, rather than just a species difference. The comparatively large effect of changes in body water on the serum sodium concentration could obscure the effects of osmotic activation, whereas the comparatively small effect of changes in sodium and potassium balance would amplify these effects. The fact that changes in sodium and potassium balance have a smaller effect on the serum sodium concentration in humans with chronic hyponatremia than they do in pigs with acute hyponatremia could imply that with a more chronic disturbance, endogenous sodium mobilized from stores, mitigates the decrease of the serum sodium concentration. Another adaptive response to hyponatremia is the so-called regulatory volume decrease (RVD) in which cellular swelling is avoided by extrusion of cell solute. A critically important adaptation in the brain, RVD has not been extensively studied in cells outside the central nervous system. As part of the RVD, extrusion of nonelectrolyte solutes (organic osmolytes) from cells into the extracellular fluid (ECF) would be expected to reduce the serum sodium concentration by increasing ECF water without changing the quantity of ECF sodium. Thus, RVD might be expected to have its most pronounced effects in earliest stages of the adaptation to hyponatremia, whereas activation of sodium stores might be the dominant response in chronic hyponatremia (12).

In a comprehensive review that should be required reading for anyone interested in body fluid physiology, Bhave and Neilson explain recent findings that have complicated our classic understanding of the physical forces that determine fluid movement across capillary and cell membrane barriers (14). Formulas like the Edelman equation that attempt to predict the changes in serum sodium concentration that occur in response to a change in sodium, potassium, and/or water balance are predicated on the assumption that an osmotic gradient between plasma, interstitial fluid, and cells can only persist if the excess sodium and potassium in the cellular or interstitial compartment are osmotically inactive. The relatively small fractions of sodium in bone and potassium in cells are called “unexchangeable” in Edelman’s equation and they are ignored and considered constant and osmotically inactive. However, an osmotic gradient is possible with osmotically active excess cation in one compartment if that were counterbalanced by the loss of nonelectrolyte osmolytes or if a hydrostatic pressure matched and opposed the osmotic pressure gradient between compartments. However, a growing literature suggests that excess sodium accumulating in cartilage permits such osmotic gradients. Cartilage is hypertonic (i.e., its sodium concentration is higher than that of plasma), but cartilage swelling is prevented by a cartilage-based hydrostatic pressure that opposes the osmotic pressure
gradient. Sodium associated with polyanionic glycosaminoglycans in cartilage and skin serves as a hypertonic solute pool that can accumulate excess sodium without expanding the plasma volume to cause hypertension, or, as has been hypothesized for runners with acute water intoxication, contribute sodium to the plasma, mitigating against both intravascular volume depletion and hyponatremia and cell swelling.

The traditional formula for electrolyte-free water clearance, which has been used to predict changes in the serum sodium concentration caused by urinary water losses, ignores the intercept of the Edelman equation. Nguyen and Kurtz derived a modified formula that takes this intercept into account (15). The traditional formula is based on the urine to plasma electrolyte ratio: Urine [Na + K]/Plasma [Na]. The modified formula adds the intercept to the denominator of the urine to plasma electrolyte ratio: Urine [Na + K]/Plasma [Na] + 23.8.

One would predict mathematically that the difference between the two formulas would be greatest in patients with hyponatremia because as the serum sodium concentration falls, the intercept becomes a proportionally greater component of the denominator. Lindner et al. obtained data on 138 critically ill patients studied over several days (16). As would be predicted mathematically, their data show that differences between the traditional and modified formulae for electrolyte-free water clearance were negligible in patients with normonatremia and hypernatremia but in hyponatremic patients the difference could be >400 ml/24 h. Calculated changes in the serum sodium concentration differed from the actual measured changes in serum sodium concentration for both formulae; the modified formula showed a trend for greater accuracy, particularly in patients with hyponatremia, but this did not reach statistical significance.

**SIADH in Runners.** Although the evidence is scanty, increased levels of ADH provoked by nonosmotic stimuli (nausea, organic stress, pain and endorphins, hypovolemia, and increased body temperature) appear to play an important role in the pathogenesis of EAH. It has been suggested that cytokine release (IL-6) could also be involved in the nonosmotic stimulation of ADH.

Recent studies of copeptin, the C-terminal fragment of the vasopressin hormone have been suggested as a surrogate marker for vasopressin release. Balanescu et al. found a significant correlation between AVP and copeptin levels over a wide range of plasma osmolalities in 20 volunteers studied under basal conditions and after water loading and hypertonic saline infusion (17). Hew-Butler et al. measured arginine vasopressin and copeptin levels in 6 hyponatremic and 20 normonatremic runners before and after three endurance runs and found that despite a 2 mEq/L decrease in serum sodium concentration, vasopressin and copeptin levels increased approximately 3-fold (11). Significant correlations were found between vasopressin and copeptin levels, leading the authors to conclude that copeptin seems to be a reliable surrogate of stimulated AVP during exercise. Although the number of patients studied was small, the data are consistent with the hypothesis that nonosmotic vasopressin stimulation occurs during ultradistance running.

**Treatment of EAH**

A rapid fall in the serum sodium concentration to levels <128 mEq/L is often associated with the emergence of serious neurologic symptoms (confusion, vigilance disorders, coma, and tonic-clonic seizures) that reflect brain swelling, as was seen in the patient described in the beginning of this discussion. Life-threatening cerebral edema may be accompanied by neurogenic pulmonary edema and the resulting hypoxia impairs brain adaptations to osmotic swelling leading to a vicious cycle that may end in death. As hyponatremia develops within a few hours, giving little time for brain adaptation, there should be a very low risk of osmotic demyelination syndrome in EAH, and no cases of osmotic demyelination syndrome have been reported despite rapid correction that often ensues when transient SIADH resolves. In this disorder, hypertonic saline should be given aggressively, beginning in the field. Bolus therapy with 100 ml of 3% saline, repeated twice if symptoms persist at 10-minute intervals, was recommended by a consensus conference.

Rogers et al. conducted a small prospective randomized controlled trial comparing 100 ml 3% saline given intravenously (n=5) to the same dose given orally (n=3) to runners competing a 161-km endurance run with asymptomatic hyponatremia (3). The serum sodium increased by 3.9±2.9 mEq/L from 130.8 to 134.6 mmol/L over the 60 minutes after intravenous hypertonic saline
(P<0.05). The increase in serum sodium averaged 0.7±0.6 mEq/L in the oral group, which, not surprisingly given the small sample size, was not significant. Elevated AVP concentrations averaging 3.9 and 3.0 pg/ml were seen at race finish in both groups and remained elevated after treatment with hypertonic saline.

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Case 4: Hyponatremia

A 55-year-old man with a history of pituitary surgery for a nonfunctional pituitary macroadenoma 10 years previously and no other medical or psychiatric problems is admitted because of several days of anorexia, nausea, and vomiting, progressing to confusion, lethargy, and disorientation to time and place. In the emergency department, he has two generalized tonic-clonic seizures.

The patient’s laboratory data are as follows: serum sodium, 102; serum potassium 4; serum chloride, 74; CO₂, 22 mmol/L; BUN, 5 mg/dl (1.8 mmol/L); creatinine, 0.5 mg/dl (44.2 μmol/L); urine osmolality, 500 mosm/kg; urine sodium, 78; and urine potassium, 50 mmol/L. His results also showed low levels of adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), and luteinizing hormone (LH).

During the patient’s hospital course, he is treated with diphenhydantoin, hydrocortisone, and isotonic saline. Eight hours later, his serum sodium increases to 115 mEq/L and his mental status improves. He is discharged 6 days later with a serum sodium of 131 mEq/L. The patient returns the next day with complaints of tremors and difficulty speaking and swallowing and is readmitted. He is fully conscious and oriented with a clear sensorium, but is irritable, suspicious, and restless, pacing the halls in anger, and accusing others of talking about him and teasing him with their gestures.

A magnetic resonance imaging (MRI) scan shows hyperintensities in the pons and bilateral basal ganglia (caudate and putamen).

Which ONE of the following statements is true about this patient?
A. Based on the patient’s symptoms, he most likely became hyponatremic because of polydipsia related to an underlying psychosis.
B. Patients like this presenting with a serum sodium concentration <110 mEq/L have an expected mortality >50%.
C. The patient has pontine and extrapontine myelinolysis and his condition is likely to progress to death or to a permanent vegetative state.
D. The patient’s behavioral symptoms, tremors, and difficulty swallowing are most likely related to steroid-induced rapid correction of hyponatremia and they may resolve with time.

Discussion

The correct answer is D. Initially presenting with hyponatremia caused by panhypopituitarism, this patient subsequently developed central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) when his electrolyte disturbance corrected rapidly in response to steroid replacement (1). CPM/EPM, also known as osmotic demyelination syndrome (ODS), has been associated with behavioral disturbances and these symptoms as well as the tremors and dysphagia are likely to improve, and, in many cases, completely resolve.

Several aspects of this patient’s course deserve further discussion: (1) the prognosis of severe hyponatremia; (2) the association of hyponatremia with often unsuspected panhypopituitarism or Addison’s disease and its susceptibility to unintentional overcorrection; (3) prevention of unintentional rapid correction of hyponatremia; (4) the pathogenesis of osmotic demyelination; (5) hyponatremia in polydipsic patients with psychiatric disease; (6) behavioral and other atypical manifestations of pontine and extrapontine myelinolysis; and (7) the prognosis of the osmotic demyelination syndrome, which is much better than once thought.

Prognosis of Severe Hyponatremia

Even mild hyponatremia is associated with increased mortality in both ambulatory and inpatient settings with a variety of underlying diseases, including heart failure, hepatic cirrhosis, kidney disease, critical illness, and so forth (2–15). The reason for a long-term mortality risk with chronic hyponatremia is unknown; however, there is increasing evidence that prolonged hyponatremia has many adverse consequences even in patients who appear to be asymptomatic. Chronic hyponatremia is associated with gait disturbances, increased falls, and bone fragility in humans, and it causes increased bone resorption in vitro and reduced bone mineral density in young rats. In a model of chronic syndrome of inappropriate antidiuretic hormone secretion (SIADH) to study multiorgan consequences of chronic hyponatremia, Barsony et al. induced and maintained hyponatremia in the rat for 18 weeks (16). In addition to marked decreases in bone density, hyponatremic rats developed hypogonadism, decreased body fat, skeletal muscle sarcopenia by densitometry, and cardiomyopathy manifested as increased heart weight and perivascular and interstitial fibrosis by histology. The authors conclude that low extracellular sodium concentrations increase oxidative stress, thereby potentially exacerbating multiple manifestations of senescence.

Several studies have found that the short-term risk of death in patients admitted to the hospital increases with the severity of hyponatremia; however, the statistical evidence for this trend is driven by the large number of patients with very mild hyponatremia, whereas there were very few patients whose serum sodium concentrations were <120 mEq/L.

Chawla et al. examined the relationship between the serum sodium concentration and the risk of mortality in a retrospective study of 45,693 patients admitted to a single community teaching hospital between January 1996 and December 2007 (17). Consistent with previously published studies, mortality rates tended to increase as the serum fell from 134 to 120 mEq/L, rising above 10% for patients with serum sodium concentrations between 120 and 124 mEq/L. However, below serum sodium of 120 mEq/L, the trend reversed, so that as the serum sodium concentration fell to lower and lower levels, the mortality rate paradoxically fell (Figure 4-1). Among the 193 patients with a serum sodium <115 mEq/L, the mortality rate (6.8%) was considerably lower than the mortality among the 1844 patients with a serum sodium between 120 and 124 mEq/L (11.2%). Detailed chart reviews of all

patients with a serum sodium $<120$ mEq/L and all patients surviving after presenting with a serum sodium $<110$ mEq/L suggested a possible explanation for the paradox. More than two thirds of patients who died after serum sodium fell below $120$ mEq/L had at least two additional acute severe progressive illnesses, most commonly sepsis and multiorgan failure. Only three deaths (5.6%) in 12 years could plausibly be related to adverse consequences of hyponatremia. The only patient to die from cerebral edema (1.8% of the fatal cases and 0.15% of all patients with serum sodium $<120$ mEq/L) had suffered a stroke after a carotid endarterectomy. Most patients who survived with serum sodium $<110$ mEq/L had medication-induced hyponatremia and severe underlying illnesses were uncommon in this group. Survival among patients with a serum sodium $<110$ mEq/L could not be attributed to aggressive therapy. The increase in serum sodium concentration during the first 24 hours averaged $9.3 \pm 3.8$ mEq/L. The findings confirmed an earlier study from the same medical center, which reported a mortality rate of only 5% among patients with a serum sodium $\leq 105$ mEq/L; the only patient who died had developed osmotic demyelination after rapid correction (18).

Seizures are a legitimate concern in patients who present with profound hyponatremia, but the true risk is lower than what is often believed. Halawa et al. studied the association between different levels of hyponatremia and the occurrence of epileptic seizures in patients without a prior epilepsy diagnosis (19). Of 150 patients with a serum sodium of 120–124 mEq/L, only 1 patient (0.6%) had a seizure. Using 120–124 mEq/L as reference, odds ratios for having seizures at serum sodium levels of 115–119 mEq/L were 3.85 (95% confidence interval [95% CI], 0.40 to 37.53), 8.43 (95% CI, 0.859 to 82.85) at 110–114 mEq/L, and 18.06 (95% CI, 1.96 to 166.86) at $<110$ mEq/L.

**Hyponatremia Due to Adrenal Insufficiency**

As emphasized in a recent review, adrenal insufficiency is an important although uncommon cause of hyponatremia (20). Addison’s disease (primary adrenal insufficiency) often presents with obvious clinical signs such as pigmentation, salt craving, hypotension, and hyperkalemia, whereas secondary adrenal insufficiency, caused by diseases of the hypothalamus and/or pituitary (hypopituitarism), typically presents with more subtle clinical signs; however, the diagnosis of both diseases is often delayed for years (21–26). Both disorders can cause hyponatremia and both can be mistaken for SIADH.

Addison’s disease affects the adrenal cortex as a whole with deficiencies of cortisol, aldosterone, and adrenal androgens. In Europe and the United States, most cases (75%–80%) are caused by autoimmune adrenalitis, which is often associated with other autoimmune disorders, and the remaining cases are due to infections (tuberculosis and AIDS), metastatic carcinoma, medications, and vascular events. In secondary adrenal insufficiency, impaired release of corticotropin-releasing hormone and/or ACTH leads to low or absent levels of ACTH and markedly reduced cortisol secretion while aldosterone levels are normal because mineralocorticoid secretion is under the control of angiotensin II rather than ACTH. Adrenal suppression from chronic steroid use is the most common cause of secondary adrenocortical insufficiency; other causes include pituitary or hypothalamic tumors (primary or metastatic, mainly breast or lung cancers), infections (tuberculosis and histoplasmosis), pituitary surgery or radiation, empty sella syndrome, and lymphocytic hypophysitis. Hypopituitarism caused by space-occupying lesions usually presents with $>1$ pituitary hormone deficiency, but isolated corticotrophin (ACTH) deficiency can occur, especially after traumatic injury or in patients with lymphocytic hypophysitis.

Because cortisol is a physiologic tonic inhibitor of ADH secretion, hyponatremia in patients with hypopituitarism is due to inappropriate secretion of ADH caused by hypocortisolism. Hypersecretion of ADH may be partly due to reduced systemic BP and cardiac output or, possibly, to increased renal sensitivity to ADH. Aquaporin-2 water channels have been shown to be upregulated in glucocorticoid-deficient rats. In addition to mechanisms related to ADH, decreased distal fluid delivery to the diluting segments of the nephron may play a role in the pathogenesis of hyponatremia associated with glucocorticoid deficiency.

Hypopituitarism presents with clinical features of SIADH, including euvolemic hyponatremia, low serum uric acid and BUN, and high urine sodium concentration. The diagnosis should be strongly considered in patients aged $\geq 65$ years who present with SIADH. It has been reported that 40% of hyponatremic patients in this age group have dysfunction of their
pituitary-adrenal axis. Hyponatremia due to adrenal insufficiency can sometimes be differentiated from other causes of SIADH by the presence of a low plasma bicarbonate level (probably because of aldosterone deficiency) (27).

A recent case report illustrates how primary adrenal insufficiency as well as secondary adrenal insufficiency can mimic SIADH (28). A young woman with pulmonary emboli caused by antiphospholipid syndrome became hyponatremic in the hospital while receiving intravenous fluids. Adrenal hemorrhage caused by thrombosis of the adrenal veins was identified as the cause. Except for a mild normal anion gap metabolic acidosis, her laboratory data (low plasma osmolality, high urine osmolality, high urine sodium concentration) could easily be mistaken for SIADH due to stress. Like approximately 30%–50% of patients with Addison’s disease, the patient was not hyperkalemic. The absence of hyperkalemia in addisonian patients can be ascribed to low dietary potassium intake, gastrointestinal losses of potassium due to anorexia, pain, and vomiting, which are common symptoms in Addison’s disease. Gagnon and Halperin postulated that cationic substances may circulate in patients with Addison’s disease caused by autoimmunity or cancer, activating the calcium-sensing receptor in the thick ascending limb of the loop of Henle and inducing a furosemide-like effect with natriuresis and also kaliuresis (29).

The patient described in the case report was neither hyperkalemic nor hypotensive. Hypotension from aldosterone deficiency will be masked by volume expansion from intravenous fluids (which will also militate against hyperkalemia). A large sodium deficit does not always cause hypotension in addisonian patients who are hyponatremic; it has been suggested that by compressing the interstitial space, thereby raising interstitial pressure, muscle cell swelling caused by hyponatremia might favor fluid movement from the interstitium to the vascular space.

A firm diagnosis of adrenal insufficiency depends on endocrine testing (20). A morning (at 8–9 a.m.) serum cortisol concentration ≥19 µg/dl (525 nmol/L) virtually rules out adrenal insufficiency, whereas concentrations ≤3 µg/dl (83 nmol/L) are highly suggestive of the diagnosis. A rise in serum cortisol concentration to a peak of 18–20 µg/dl (497–552 nmol/L) or more, 30–60 minutes after the intravenous administration of 250 µg of corticotrophin, indicates a normal response to the high-dose ACTH stimulation test and excludes primary adrenal insufficiency and most patients with secondary adrenal insufficiency. However, in mild or recent-onset secondary adrenal insufficiency, the test may be normal because the large dose of ACTH that is given (250 µg) possibly represents a supraphysiologic stimulus leading to stimulation of a partially diseased adrenal. In such cases, additional testing with insulin-induced hypoglycemia or metyrapone tests may be necessary. However, both of these tests can precipitate an acute adrenal crisis, and insulin-induced hypoglycemia testing is contraindicated in patients with coronary artery disease, epilepsy, and age >60 years. A low-dose (1 µg) ACTH stimulation test is another option for patients with suspected secondary adrenal insufficiency. A serum cortisol concentration ≤18–20 µg/dl (497–552 nmol/L), 30 minutes after the intravenous administration of 1 µg of corticotrophin, establishes the diagnosis of secondary adrenal insufficiency in nonstressed patients.

In critically ill patients (e.g., with severe sepsis, major trauma), a serum cortisol value in the normal range does not rule out adrenal insufficiency. A random serum cortisol concentration >25 µg/dl (700 nmol/L) makes the diagnosis highly unlikely and a cortisol level ≤25 µg/dl after a low-dose ACTH stimulation test or a rise over baseline <9 µg/dl (250 nmol/L) represents an inadequate adrenal response.

In primary adrenal insufficiency, serum ACTH is >100 pg/ml (22 pmol/L), and secondary adrenal insufficiency is associated with a low-normal serum ACTH concentration. A serum ACTH value within the normal range is inappropriately low in a stressed patient and supports the diagnosis of secondary adrenal insufficiency. In Addison’s disease, serum renin is increased because of the sodium wasting, and serum aldosterone concentration is low or low normal because the adrenal gland cannot produce it. Serum levels of renin and aldosterone are usually unaffected in secondary adrenal insufficiency, except for some cases of very prolonged deficiency of ACTH.

Susceptibility to Rapid Correction of Hyponatremia in Adrenal Insufficiency

Hyponatremia due to either primary or secondary adrenal insufficiency is susceptible to rapid correction after steroid replacement (30, 31). Administration of cortisol restores the normal tonic inhibition of vasopressin release from the hypothalamus, allowing the
hormone to respond to what should normally be an inhibitory osmotic stimulus (hyponatremia). Once normal physiology is restored, vasopressin levels fall to undetectable levels in response to hyponatremia, and the urine becomes maximally dilute, increasing urine output to >500 ml/h, which increases the serum sodium concentration by >2 mEq/L per hour. In Addison’s disease, the water diuresis will not occur until correction of hypovolemia with intravenous fluids removes a hemodynamic stimulus for vasopressin secretion, allowing a larger fraction of the glomerular filtrate to escape proximal reabsorption reaching diluting sites in the distal nephron. Several cases of osmotic demyelination have been reported in this setting (1,30,32,33).

**Avoiding Neurologic Injury from Rapid Correction of Hyponatremia**

Steroid replacement in adrenal insufficiency is just one of several settings in which potentially dangerous unintentional rapid correction of hyponatremia may occur. In many patients with hyponatremia, the ability to excrete dilute urine is reversibly impaired. Once the cause of water retention resolves, the ability to excrete dilute urine is restored and the serum sodium increases rapidly because of the resulting water diuresis. Examples of this phenomenon include hyponatremia caused by hypovolemia, poor solute intake (e.g., beer potomania), thiazide diuretics, and spontaneous resolution of a reversible cause of SIADH (e.g., nausea, hypoxia, recent surgery, or medications that induce SIADH).

Kamel and Halperin have emphasized the important role that enhanced distal delivery of solute plays in the recovery of hyponatremia associated with hypovolemia and/or poor dietary solute intake (34). Limited distal delivery can allow chronic hyponatremia to develop even if vasopressin is absent. It was once thought that approximately two thirds (66%) of the glomerular filtrate is reabsorbed in the proximal nephron. Recent evidence, derived from micropuncture in rats, lithium clearance in humans, and a new understanding of the expression of aquaporin 1 (and therefore water permeability) in the descending thin limb of the loop of Henle, suggest that five sixths (83%) of the GFR is normally reabsorbed in the proximal convoluted tubule. In an elderly woman taking a thiazide diuretic who is deprived of dietary protein and salt, proximal reabsorption might increase to 90% of the GFR. If that patient’s GFR were only 30 ml/min (40 L/d) because of hypertensive nephrosclerosis, only 4 L of filtrate would reach the distal tubule; even in the absence of vasopressin, much of that fluid would be reabsorbed by the inner medullary collecting duct because of its residual water permeability coupled with differences in osmolality between luminal fluid (because of the patient’s low osmole excretion rate) and the medullary interstitium. It is easy to understand why hyponatremia would develop at a water intake of >2–3 L daily. Even modest amounts of isotonic saline in this setting would be expected to increase distal delivery of filtrate, theoretically increasing distal delivery to 6.8 L per day (83% of 40 L of filtrate), allowing a water diuresis to occur. With a small muscle mass, even a modest water diuresis is large enough to cause a rapid rise in serum sodium concentration.

One author suggested using very low steroid replacement doses in hyponatremic patients with adrenal insufficiency to avoid precipitating a water diuresis (35). An analogous strategy would be to limit isotonic saline or transfusion in patients who are hyponatremic because of hypovolemia. However, a better strategy would be to aggressively treat the patient’s adrenal insufficiency or hypovolemia and use other measures to address the problem of unintentional overcorrection that might result from these therapies.

If a water diuresis is causing the serum sodium to increase too rapidly in a chronically hyponatremic patient with a serum sodium <120 mEq/L, there are two major options: (1) match urinary water losses with 5% dextrose in water, and (2) administer 2–4 µg of parenteral desmopressin to stop the water diuresis (36,37).

We believe the latter strategy to be less labor intensive and generally more successful in preventing overcorrection. If the increase in serum sodium concentration has already exceeded 10–12 mEq/L within 24 hours or if it has exceeded 8 mEq/L in a patient with major risk factors for ODS (hypokalemia, serum sodium <105 mEq/L, alcoholism, malnutrition, or liver disease), relowering of the serum sodium concentration has been recommended (36,37). Administration of desmopressin with concurrent hourly infusions of 3 ml/kg 5% dextrose in water with hourly serum sodium terminations between infusions will lower the serum sodium concentration by approximately 1 mEq/L per hour and these are continued until the serum sodium reaches a level 8 mEq/L higher than...
the previous day’s level. Although experience with therapeutic relowering of the serum sodium is limited, the maneuver has been well tolerated.

A more proactive strategy to avoid overcorrection has recently been reported (38). The regimen is particularly attractive in patients with known or suspected adrenal insufficiency who require steroid replacement; in this setting, as in patients with hyponatremia caused by hypovolemia or medications, an eventual water diuresis is almost inevitable, but there is no way to predict when it will occur. Rather than giving desmopressin to stop a water diuresis after it has already begun, desmopressin was administered at the beginning of therapy along with 3% saline to achieve a controlled rate of correction. Desmopressin creates a state of stable, iatrogenic SIADH. The clinician then controls the increase in serum sodium concentration by titrating the amount of sodium given to the patient as 3% saline, and the amount of potassium given as oral KCl, or 400 mm KCl (KCl given at a concentration of 100 mmol/L does not increase the serum sodium concentration). The regimen eliminates the unpredictable variable of urinary water losses. Sood et al. reported their experience with desmopressin/3% saline in 25 consecutive patients with serum sodium concentrations <120 mEq/L who were treated in a single community teaching hospital (38). The regimen successfully avoided correction by ≥12 mEq/L in 24 hours and ≥18 mEq/L in 48 hours in all patients (Figure 4-2). The increase in serum sodium concentration during the first 2 days of therapy averaged 5.8±2.8 and 4.5±2.2 mEq/L, consistent recently recommended targets for safe correction of hyponatremia (36). The increase in serum sodium due to the infusion of 3% saline did not differ significantly from the increase predicted by the Adrogue-Madias formula.

Hypertonic saline is avoided in some centers because of the mistaken belief that it must be administered in a central vein. There is no evidence to support the practice and a standard textbook on intravenous medications used by hospital pharmacies no longer recommends that hypertonic saline be given only in a central vein. In the aforementioned series, all patients received hypertonic saline in a peripheral vein without incident. Similarly, in a recent series of 56 pediatric patients treated in an emergency room with 3% saline for hyponatremic emergencies, 87% of doses were administered without complication in a peripheral vein (39).

Severely hyponatremic patients with kidney failure pose a special problem because the serum sodium concentration can be expected to increase rapidly if the patient is treated with conventional hemodialysis (40). In experimental models, uremic animals are less likely to develop osmotic demyelination after rapid correction of hyponatremia than animals without kidney failure. In addition, dehydration of brain cells caused by a rising serum sodium concentration during dialysis would be expected to be countered by brain swelling caused by a falling BUN. Although there is a clinical impression that uremic patients with hyponatremia seem to tolerate rapid increases in the serum sodium concentration, there have been a few case reports of ODS complicating hemodialysis. Therefore, large increases in the serum sodium during dialysis should be avoided if possible. Because dialysate sodium concentrations cannot be reduced <130 mEq/L with available equipment, blood flow should be markedly reduced (to approximately 1 ml/kg body weight per minute) and dialysis time should be shortened if the serum sodium is <120 mEq/L. If one assumes 100% equilibration of sodium between the dialysate (130 mEq/L) and the patient’s blood at the initiation of dialysis, the amount of sodium transferred to the patient will equal the blood flow in liters per hour multiplied by the difference between plasma and dialysate sodium concentrations (41). These assumptions were validated in a recent case report of a 50-kg elderly woman with a serum
sodium concentration of 113 mEq/L who was dialyzed against a 130 mEq/L sodium bath for 3 hours at a blood flow rate of 50 ml/min (3 L/h or 9 L in a 3-hour session), using the pediatric mode of the dialysis machine (41). The serum sodium concentration increased by 6 mEq/L during dialysis, matching the authors’ predictions (based on total body water of 25 L):

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\text{Sodium transferred to patient} = (130 - 113) \text{mEq/L} \times 9 \text{ L} = 153 \text{ mEq}
\]

Increase in serum sodium concentration

\[
= 153 \text{ mEq}/25 \text{ L} = 6 \text{ mEq/L}
\]

For patients with extremely low serum sodium concentrations, a form of continuous renal replacement therapy can be used. In this case, sodium concentration of the replacement fluid or dialysate can be adjusted to be a few milliequivalents per liter higher than the patient’s serum sodium concentration (42).

**Pathogenesis of Osmotic Demyelination**

Osmotic demyelination has been reproduced in experimental models of chronic (3 days) but not acute (<1 day) hyponatremia in dogs, rats, and rabbits. Osmotic demyelination does not complicate uncorrected hyponatremia and brain lesions are more severe and more likely to occur with faster rates of correction. Relowering the serum sodium concentration after rapid correction is protective against myelinolysis, lending further support to the conclusion that the disease is caused by correction of hyponatremia rather than by complications of hyponatremia itself, like hypoxia (43). Relowering the serum sodium concentration has also been reported to reverse the clinical manifestations of osmotic demyelination in humans.

In chronic hyponatremia, brain volume remains normal because of an adaptive loss of solute—sodium, potassium, and organic osmolytes (osmotically active small molecules). When chronic hyponatremia is corrected too rapidly, brain sodium content rapidly increases, exceeding normal levels, while the reaccumulation of organic osmolytes occurs very slowly. Areas of the brain that are the slowest to reaccumulate osmolytes have been shown to suffer the greatest injury, but the mechanisms connecting impaired osmolyte reaccumulation, myelin loss, and the cells involved in this process have not been well established.

Astrocytes appear to be responsible for regulating brain water content and organic osmolyte homeostasis; they are in close contact with blood vessels, and *in vitro* studies show that these cells regulate organic osmolyte fluxes during anisosmotic conditions. Depletion of organic osmolytes during correction of chronic hyponatremia may play a role in astrocyte death in ODS (44). Regions of astrocyte cell loss correspond to the distribution of organic osmolyte transporters in the rat brain and the degree of osmolyte depletion during chronic hyponatremia. Administration of the osmolyte, myoinositol is protective against ODS in the rat, and the osmolyte prevents the death of astrocytes exposed to hyperosmolality *in vitro* (45). Connexins connect astrocytes to each other and to oligodendrocytes in a glial syncytium that is needed for normal myelination. Rapid correction of chronic hyponatremia results in early changes in the astrocyte-oligodendrocyte gap junction complex, which may contribute to demyelination in ODS. Astrocyte death is also associated with local disruption of the blood–brain barrier, which has been shown to play a role in the pathogenesis of ODS.

Activated microglia appear after astrocyte loss and their role in the demyelinating lesions is not clear. Some investigators believe these cells to be responsible for demyelination, whereas others suggest that microglia are activated by the inflammatory mediators produced during astrocyte death serve as scavengers of myelin debris (46,47).

**Hyponatremia in Psychiatric Patients with Polydipsia**

In the patient described at the beginning of this discussion, psychosis was a consequence of the treatment of his hyponatremia and not the cause of his hyponatremia. Hyponatremia due to self-induced water intoxication is common among institutionalized schizophrenics with polydipsia, but that is an unlikely cause of hyponatremia in a 55-year-old man with no prior history of psychiatric disease. Polydipsia may be present in >20% of chronic psychiatric inpatients; up to 5% develop clinically apparent water intoxication, although mild cases may go undetected (48). Psychotic patients with severe polydipsia may periodically ingest over a liter of water an hour, a rate that exceeds the kidney’s ability to excrete electrolyte-free water (49).

Severe delirium or seizures often emerge because of the resulting rapid fall in the serum sodium concentration of 113 mEq/L who was dialyzed against a 130 mEq/L sodium bath for 3 hours at a blood flow rate of 50 ml/min (3 L/h or 9 L in a 3-hour session), using the pediatric mode of the dialysis machine (41). The serum sodium concentration increased by 6 mEq/L during dialysis, matching the authors’ predictions (based on total body water of 25 L):
concentration; patients subsequently begin to excrete large volumes of dilute urine and the serum sodium concentration often returns rapidly to normal. Despite a high incidence of seizures from hyponatremia, clinically obvious adverse neurologic outcomes after rapid correction of self-induced acute water intoxication are unusual (50).

However, self-induced water intoxication due to schizophrenia is not a benign disorder. Deaths from acute cerebral edema have been reported. In addition, imaging studies of polydipsic hyponatremic schizophrenia patients have shown volume reductions in the anterior medial temporal lobe compared with non-polydipsic schizophrenic controls (51).

Hyponatremic patients had poorer neuropsychologic functioning compared with patients without a water imbalance. Compared with controls, polydipsic hyponatremic schizophrenia patients have significantly impaired visual memory and information processing, intelligence, learning/memory, and facial discrimination. Structural changes in the anterior hippocampus, as well as in the associated prefrontal/limbic brain regions, are believed to contribute to the underlying pathophysiology of polydipsic hyponatremic schizophrenia, although it is unclear whether these structural changes are the cause or the result of hyponatremia and/or its rapid correction.

Behavioral and Other Atypical Symptoms of CPM/EPM

CPM is a demyelinating disorder affecting the pons characterized by an acute progressive quadriplegia, dysarthria, dysphagia, and altered consciousness. These clinical features reflect prominent demyelination in the central pons with sparing of axons and neurons. Frequently, CPM is associated with EPM in other areas of the brain that can be associated with a variety of symptoms and findings (32,52,53). Demyelinating lesions of the basal ganglia result in parkinsonian symptoms such as rigidity of limbs, bradykinesia, tremors, and decreased blinking. Basal ganglia involvement in Wilson’s disease and Parkinson’s disease can be associated with psychotic symptoms and this is also true of extrapontine myelinolysis. Reported behavioral manifestations are personality change, inappropriate affect, emotional lability incontinence, disinhibition, poor judgment, catatonic syndrome, and delirium. Subcortical demyelination may also be responsible for some of these symptoms (53,54).

A recent single-center series showed that extrapontine lesions are much more common that has been reported in the past and may be more common than classic CPM (32). Over the course of a year, eight patients developed ODS after treatment of hyponatremia due to various etiologies, including one case complicating postpartum pituitary hemorrhage. Neurologic symptoms of ODS emerged in a typical biphasic pattern beginning 3–15 days after clinical improvement in four patients; the others did not show any intervening lucent interval. Two thirds of patients had features of parkinsonism and MRI showed symmetric striatal lesions in all patients, with concomitant pontine involvement in only 25%. Parkinsonian symptoms responded to dopaminergic therapy, with chorea, dystonia, and depression as later developments.

A recent series of 12 patients with osmotic demyelination identified at a single tertiary medical center reported similar findings (53). Of the 10 patients with plasma sodium levels that were known, 1 patient had severe acute hypernatremia (176 mEq/L due to a dialysis error) and 6 patients had severe hyponatremia (<110 mEq/L in 4 patients) that had been corrected rapidly. Patients with symptomatic hyponatremia initially improved after treatment, but then with a delay of 3–15 days a variety of neurologic complications developed, including rigidity, cardiorespiratory symptoms, autonomic dysfunction, seizures (generalized tonic-clonic and partial complex), altered consciousness, pyramidal, brainstem and cerebellar signs, and neuropsychiatric problems (catatonia, emotional lability). As reported previously, two patients had negative MRI scans 2–3 days after clinical manifestations of ODS, only to have subsequent positive results on studies 10 and 26 days later. Only two of the hyponatremic patients were known to be alcoholics. Two patients developed hyponatremia as a complication of the treatment of diabetes insipidus and corrected rapidly when desmopressin was stopped. Correction in the hyponatremic patients exceeded 18 mEq/L within 48 hours in all patients and it exceeded 25 mEq/L in 48 hours in only three patients.

Recovery of CPM/EPM

Several studies have reported full recoveries from CPM/EPM, a disorder that was once thought to have a dismal prognosis. A series of 24 patients identified at the Mayo Clinic over the course of 11 years found a favorable outcome in 60%, with an overall mortality
of 8% in the acute setting (55). Another recent study of 25 patients found that 46% achieved a favorable outcome (56). The increasing availability of MRI scans aiding in early diagnosis are likely contributing factors to these improvements in outcome (57). In a review of 76 pediatric cases that have been reported in the literature, Ranger and coworkers found that the diagnosis, course, and outcomes have changed over the past few decades. Because early cases were diagnosed at autopsy rather than by imaging, the mortality rate in the literature was 94% before 1990 and only 7% from 1990 to the present (58). The decade in which the case was reported was the strongest predictor of outcome. Even severe cases of CPM/EPM can recover. A study conducted in 46 French intensive care units identified 36 patients with central or extrapontine myelinolysis treated between 2000 and 2010 (59). Of these, 31 patients (86%) were alcoholics, 33 (92%) initially presented with hyponatremia, and 32 (89%) required mechanical ventilation. About one third of patients died in the first year, but 14 survivors (56%) returned to a Rankin score ≤1, indicating minimal or no disability. Disturbingly, life-supporting therapies were withheld in 11 patients (31%) because of severe cerebral motor disability. However, 5 of the 11 patients who were withdrawn from life support were still alive at 1 year, 4 of them with a Rankin score ≤1. There was no statistical difference between the severity of illness for the 18 patients (50%) with a favorable outcome and the 18 patients (50%) with an unfavorable outcome. These findings indicate that recovery from severe ventilator-dependent CPM/EPM is likely and that for an individual patient, the prognosis cannot be predicted on the basis of clinical presentation. Aggressive supportive care should continue for most patients for several weeks before concluding that the situation is hopeless.

References


Case 5: Hyponatremia

A 54-year-old African-American woman with bipolar disorder treated with lithium carbonate for 20 years was admitted because of several days of progressive drowsiness and confusion. She denied nausea, vomiting, or diarrhea, and there had been no recent changes in her medications.

The patient’s physical examination showed a fine resting tremor and she was dysarthric and disoriented to time and place. She had a BP of 124/73 mmHg, heart rate of 104 beats per minute, and temperature of 37°C.

The patient’s laboratory results were as follows: serum sodium, 143; serum creatinine, 2.3 mg/dl; and serum lithium level, 2.4 mEq/L. A computed tomography changes in proinflammatory and neurotrophic responses of microglia and astrocytes in a rat model of osmotic demyelination syndrome. Glia 59: 452–462, 2011 PubMed


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The patient’s laboratory results were as follows: serum sodium, 143; serum creatinine, 2.3 mg/dl; and serum lithium level, 2.4 mEq/L. A computed tomography
(CT) scan of the head revealed only mild cerebral atrophy.

The patient’s lithium was discontinued. Twenty-four hours after admission, her mental status worsened and laboratory data were repeated. The results were as follows: serum sodium, 168 mmol/L; serum creatinine, 2.3 mg/dl; lithium, 2.2 mEq/L; urine osmolality, 147 mOsm/kg; and urine sodium, 42 mmol/L.

A diagnosis of nephrogenic diabetes insipidus was made; 200 ml of water was administered every hour by a nasogastric tube and half normal saline was infused so as to exceed the patient’s urine losses by 150 ml/h urine losses. The serum sodium decreased to normal by 1 mmol/L per hour, lithium levels returned to the therapeutic range, and she became more alert; however, serum creatinine remained elevated at 1.8 mg/dl.

A few days later, she became mute with bilateral upper extremity wrist drop and diffuse hyperreflexia with clonus.

A magnetic resonance imaging (MRI) scan of the brain showed a bright spot in the area of the pituitary and small areas of flair hyperintensity in the left splenium and body of corpus callosum, with a focus of demyelination of the left temporal lobe.

Which ONE of the following statements is true?

A. The diagnosis of nephrogenic diabetes insipidus could have been confirmed by measuring copeptin, a precursor of vasopressin.
B. The presence of a pituitary bright spot indicates that the patient has central diabetes insipidus.
C. The patient’s current neurologic findings were caused by rapid correction of hypernatremia.
D. Diabetes insipidus is likely to persist after lithium is discontinued.

Discussion

The correct answer is D. This case, which can be found in an online report (1), illustrates how quickly severe hypernatremia can develop when patients with diabetes insipidus are denied water (2–5). This patient’s low urinary osmolality despite being hypernatremic makes the diagnosis of diabetes insipidus. Nephrogenic diabetes insipidus would be expected in a patient on lithium therapy and is often permanent. In addition to the clinical setting, the presence of a pituitary bright spot, which indicates normal stores of vasopressin, is evidence against the already unlikely possibility of central diabetes insipidus. Cerebral edema caused by rapid correction of chronic hypernatremia is the most familiar neurologic complication of hypernatremia. More recently, limbic demyelination, analogous to extrapontine myelinolysis after rapid correction of hyponatremia, has been recognized as a serious complication of a rapid rise in serum sodium concentration from normal to hypernatremic levels (6).

Diagnosis of Diabetes Insipidus

The pituitary bright spot on MRI reflects vasopressin stores in the posterior pituitary; its absence can be a clue to the diagnosis of central diabetes insipidus (7). However, the water deprivation test combined with direct or indirect measurement of plasma arginine vasopressin (AVP) levels is the most widely used method for distinguishing between the various causes of polyuria (8). Unfortunately, direct measurement of AVP is hampered by technical difficulties. Copeptin, the stable C-terminal fragment of the AVP prohormone has been suggested as a more easily measured surrogate of AVP secretion. Fenske et al. studied the utility of copeptin in the diagnostic work-up of the polyuria-polydipsia syndrome in 20 healthy participants and 50 patients with polyuria (9). Participants were water restricted, plasma AVP and copeptin levels were measured, and the laboratory findings were compared with a final diagnosis based on clinical information and treatment response. Twenty-two patients (44%) were diagnosed with primary polydipsia, 17 (34%) with partial central diabetes insipidus, 9 (18%) with complete central diabetes insipidus, and 2 (4%) with nephrogenic diabetes insipidus. Use of the urine osmolality and its response to vasopressin replacement led to a correct diagnosis in 35 of 50 patients (70%). Water deprivation supplemented by AVP or copeptin measurements correctly diagnosed 23 patients (46%) or 36 patients (72%), respectively. Baseline copeptin values >20 pmol/L identified patients with nephrogenic diabetes insipidus, and concentrations below 2.6 pmol/liter indicated complete central diabetes insipidus. The ratio between the change in copeptin levels during water deprivation and the serum sodium after water dehydration yielded optimal diagnostic accuracy, permitting distinction between partial central diabetes insipidus from primary polydipsia (86% sensitivity and 100% specificity). The authors concluded that copeptin holds promise as a diagnostic tool in polyuria-polydipsia syndrome, significantly
improving the diagnostic accuracy of the water deprivation test.

However, copeptin, which is not yet commercially available in the United States, is of unproven value in the evaluation of disturbances of water balance in acutely ill patients like the case described at the beginning of this discussion, particularly when kidney function is compromised. In a secondary analysis of three previous prospective studies including patients with lower respiratory tract infections and acute cerebrovascular events, Nigro et al. found that plasma copeptin levels appear to add very little information to the work-up of sodium imbalance in medical inpatients (10). Nonosmotic stress release is a major confounder and patients with impaired kidney function have higher plasma levels of copeptin, possibly reflecting the fact that copeptin is mainly cleared by the kidneys.

**Lithium-Induced Nephrogenic Diabetes Insipidus and Chronic Kidney Injury**

Recognized for decades as a valuable treatment for bipolar disorder, recent evidence that lithium has antiapoptotic effects in the brain has led to new uses as a neuroprotective agent in stroke, traumatic brain injury, and neurodegenerative disorders. Therefore, it is likely that the drug will see expanded use in the future. Unfortunately, lithium is nephrotoxic. Nephrogenic diabetes insipidus occurs in approximately 40% of lithium-treated patients. Kishore and Ecelbarger recently reviewed the explosion of knowledge regarding the mechanisms of lithium’s effects on the kidney and the central nervous system (11).

Vasopressin-resistance of the collecting duct is likely caused by inhibition of glycogen synthasekinase-3, β isoform (GSK3β), impaired cAMP production, dysregulation of renal PGs, altered purinergic signaling, and changes in renal architecture. Chronic usage of the drug may cause CKD and, rarely, progression to ESRD. Altered expression of several acid-base transporters may cause a normal anion gap acidosis due to diminished net proton secretion in the collecting duct, excessive back-diffusion of acid, or both. Chronic lithium use causes potentially irreversible tubular atrophy and chronic interstitial fibrosis.

Lithium is freely filtered at the glomerulus and mostly reabsorbed in the proximal tubule, making it a useful marker for sodium reabsorption in the proximal tubule. The fraction that escapes proximal re-absorption enters collecting duct principal cells through the apical epithelial sodium channel (ENaC) and, by reducing the expression of a variety of principal cell proteins involved in water and salt re-absorption (aquaporin 2 [AQP2] and ENaC subunits) and urea transport (UT-A1 and UT-B), it reduces medullary interstitial osmolality. Antagonism of the ENaC by amiloride reduces lithium reabsorption by the principal cells and can limit the severity of lithium-induced nephrogenic diabetes insipidus.

Two transport processes regulated by arginine vasopressin are altered in lithium-induced nephrogenic diabetes insipidus. Lithium reduces AQP2 protein abundance, which diminishes osmotic water reabsorption in the collecting duct, as well as UT-A1 and UT-A3 protein abundances in the inner medulla, which reduces the concentration gradient of the medullary interstitium. Lithium also interferes with the AVP-induced phosphorylation of the urea transporters, a cAMP-dependent process, preventing trafficking of the UT transporters to the membrane. Further studies are needed to define the mechanisms by which lithium decreases AQP2 mRNA levels and how lithium affects cAMP-dependent processes that regulate urea transporter proteins.

Available treatments of acquired lithium-induced nephrogenic diabetes insipidus with thiazides, amiloride, or PG synthesis inhibitors have had varying degrees of success, and have many side effects. Recently, evidence of lithium interaction with prostanoid and purinergic signaling has emerged, offering the promise that targeting purinergic P2Y receptors for the treatment of lithium-induced nephrogenic diabetes insipidus might be possible.

In the last decade, it has been discovered that with chronic lithium therapy, the collecting duct undergoes “remodeling,” with an increased number of intercalated cells and a reduced number of principal cells in the inner medulla. Surprisingly, these changes are associated with a high proliferative rate of principal cells. Inhibition of GSK3β by serine phosphorylation may be the mechanism for proliferative and antiapoptotic actions of lithium in the collecting duct. Increased activity of GSK3β is proapoptotic and preserves differentiation.

**Prevention of Hypernatremia**

Hypernatremia is best managed by avoiding it. Because patients with chronic diabetes insipidus
become accustomed to their polyuria, they may not mention it when they are admitted for surgical procedures. Unrecognized nephrogenic diabetes insipidus commonly results in perioperative hypernatremia. In patients with known central diabetes insipidus, desmopressin must be continued during hospitalization, even if hyponatremia develops. If the agent is stopped and the patient is unable to replace water losses, severe hypernatremia can develop rapidly. This can be a major problem in patients who have concurrently impaired thirst due to hypothalamic disease (5,12–14).

Hypernatremia can also develop during an osmotic diuresis. This is particularly common in elderly patients with severe nonketotic hyperglycemia. Early replacement of free water losses should be begun after initial volume resuscitation if the serum sodium concentration corrected for the effect of hyperglycemia is high (15).

**Recognizing Water Losses Caused by Urea**

A urea diuresis is often missed when the serum sodium concentration is rising because the high urine osmolality can be mistaken for renal retention of free water. Traditional free water clearances have been used in the past to quantify renal water handling as follows:

Free water clearance = Urine flow rate × (1 – Urine Osmolality/Plasma Osmolality)

However, this calculation is based on osmolality, which is influenced by the concentration of the ineffective osmole, urea. If the urine osmolality is high because of high concentrations of urinary urea, one could reach the erroneous conclusion that no water is being lost in the urine (free water clearance is negative) and water replacement need not be prescribed. For example, in a patient recovering from prerenal azotemia, elimination of urea in the urine increases the urine flow rate; the serum sodium concentration rises, but a calculation of free water clearance would have suggested negative free water clearance because the urine osmolality is higher than the plasma osmolality. Similarly, in a catabolic patient becoming dehydrated, high rates of urea generation increase the urine flow rate, but a rising plasma urea concentration does not prevent the serum sodium concentration from rising; yet, owing to the actions of antidiuretic hormone, urine osmolality is higher than plasma osmolality and free water clearance is negative, misleading the clinician. Electrolyte-free water clearance (EFWC), which is determined by the tonicity of the urine rather than its osmolality avoids this error (16). The EFWC is based on the ratio of the concentration of sodium plus potassium in the urine to the plasma sodium concentration (also known as the urine to plasma electrolyte ratio):

\[
\text{EFWC} = \text{Urine flow rate} \times (1 - (\text{Urine}[\text{Na} + \text{K}] / \text{Plasma}[\text{Na}]))
\]

Linder et al. studied 69 patients with intensive care unit–acquired hypernatremia (7% of the 981 patients admitted during the study period) (17). Of these, seven patients (10% of the patients with hypernatremia) were found to have hypernatremia due to osmotic urea diuresis, which could be attributed to high protein feeding, catabolism from steroids or pressors, or recovery from azotemia. Urea was considered to be the cause of the diuresis if the urea concentration in urine was >250 mmol/L or if the contribution of urea to urine osmolality was greater than that of sodium and potassium and their accompanying anions.

As the patients were becoming hypernatremic, traditional free water clearance was negative in every case, giving the misleading impression that water was being retained. A calculation of EFWC showed correctly that in every case, water was being lost and was not being replaced. Furthermore, as the patients lost hypotonic fluid in their urine because of an osmotic urea diuresis, these losses were replaced by isotonic fluids resulting in a gain of sodium as well as a loss of electrolyte-free water.

The effect of endogenous urea excretion on the serum sodium concentration has been exploited therapeutically using parenteral infusion and/or oral administration of urea as a treatment for acute and chronic hyponatremia. Although unfamiliar to nephrologists in the United States, this treatment has become popular in Belgium. Soupart et al. recently showed that chronic oral urea therapy was as effective and as well tolerated as oral vasopressin antagonists in managing chronic hyponatremia caused by syndrome of inappropriate antidiuretic hormone secretion (18).
Correction of Hypernatremia

In chronic hypernatremia, there is concern that rapid correction can lead to cerebral edema. Maximum correction rates of 0.5 mEq/L per hour or 10–12 mEq/L per day have been recommended. These recommendations are based on animal models and observational studies in dehydrated pediatric patients who develop seizures and a bulging fontanelle when severe hypernatremia is corrected rapidly (19). There are no prospective human studies to fully validate these recommendations and no convincing evidence of adverse outcomes after rapid correction of hypernatremia in adult patients. It has generally been believed that acute hypernatremia can be corrected promptly because cerebral adaptations to hypernatremia take place over several days. It has been recommended that acute hypernatremia can be corrected by 1 mEq/L per hour, with no need for gradual correction over 2 to 3 days. However, these recommendations as well are not based on solid data.

In a single-center study conducted in a veterans hospital, Alshayeb et al. retrospectively studied consecutively 131 patients (98% men) with a serum sodium concentration ≥155 mEq/L, excluding patients with a BP <90 mmHg, to determine the association of correction rates on 30-day mortality (20). Patients who had become hypernatremic in <48 hours were considered to have acute hypernatremia, whereas those with a slower onset and those with an unknown duration of hypernatremia were considered chronic. Forty-three patients (37%) died during their hospitalization, 10 of them within 72 hours of diagnosis. Patients whose hypernatremia was corrected within 72 hours had lower mortality rates (10% versus 25%; \( P<0.01 \)) and were significantly more likely to be managed in the intensive care unit (89% versus 64%; \( P=0.01 \)), less likely to have do not resuscitate (DNR) status (21% versus 42%; \( P=0.03 \)), had higher mean arterial pressure (MAP)\( s \) (95±16 mmHg versus 86±13 mmHg; \( P=0.003 \)), and had higher first 24-hour hypernatremia correction rates (0.39±0.32 mEq/L per hour versus 0.07±0.20 mEq/L per hour) compared with patients whose hypernatremia was not corrected within 72 hours. The mean baseline serum Na\( ^+ \) concentration was similar between the two groups (160±4 mEq/L versus 159±3 mEq/L; \( P=0.15 \)). The rate of correction in the first 24 hours for the entire cohort was 0.15±0.30 mEq/L per hour (range, –0.42 to 1.38 mEq/L per hour) and the mean 72-hour hypernatremia correction rate was 0.15±0.10 mEq/L per hour (range, –0.12 to 0.36 mEq/L per hour). There was a highly significant correlation between slower rates of correction of hypernatremia (<0.25 mEq/L per hour in the first 24 hours) and mortality (\( P=0.004 \)) (Figure 5-1). The rate of correction was ≥0.25 mEq/L per hour in 39 patients (33%) and <0.25 mEq/L per hour in 78 patients (67%). Seven of 39 patients in the faster rate correction group died within 30 days (mortality rate, 18%) compared with 36 of 78 patients (mortality rate, 46%) in the slower correction group (\( P=0.003 \)) (Figure 5-1).

A univariate analysis showed that in addition to slow correction rates, DNR status, age >86 years, heart failure, neurologic impairment, heart rate >100 bpm, mean arterial pressure (MAP) <70 mmHg, and diastolic BP <60 mmHg were all significantly correlated with mortality. In a multivariate analysis, DNR status, slow serum Na\( ^+ \) correction rate in the first 24 hours and heart rate >100 bpm were independently predictive of mortality. Although mean serum sodium concentrations at the time of diagnosis were similar between the survivor and nonsurvivor groups (159±4 mEq/L versus 158±2 mEq/L), the mean rate of correction was significantly higher in the survivor group compared with the nonsurvivor group at 24 hours (0.23±0.32 mEq/L per hour versus 0.01±0.22 mEq/L per hour), 48 hours (0.15±0.14 mEq/L per hour versus 0.06±0.14 mEq/L per hour), and 72 hours (0.15±0.14 mEq/L per hour versus 0.08±0.1 mEq/L per hour). Consequently, patients who survived had significantly higher heart rates, MAPs, and diastolic pressures.

**Figure 5-1.** Kaplan–Meier curve showing 30-day patient survival rate according to the first 24-hour serum sodium correction rate. Reprinted with permission from Alshayeb HM, Showkat A, Babar F, Mangold T, Wall BM: Severe hypernatremia correction rate and mortality in hospitalized patients. *Am J Med Sci* 341: 356–360, 2011.
lower serum Na⁺ concentrations than those who died at 24 hours (154±7 mEq/L versus 158±5 mEq/L), 48 hours (151±6 mEq/L versus 155±6 mEq/L), and 72 hours (148±6 mEq/L versus 152±6 mEq/L) (Figure 5-2).

Patients with acute hypernatremia were corrected more rapidly (0.36±0.48 mEq/L per hour) than those with chronic hypernatremia (0.09±0.21 mEq/L per hour). Eleven patients with acute hypernatremia were corrected by ≥0.5 mEq/L per hour, whereas only one patient with chronic hypernatremia was corrected this rapidly. Consequently, after 72 hours, the mean serum Na⁺ concentration was normalized (144±7 mEq/L) in the acute hypernatremia group, but it remained high in patients with chronic hypernatremia (150±5 mEq/L). Hypernatremia was corrected within 72 hours in 57% of patients with acute hypernatremia compared with 19% of patients with chronic hypernatremia. Thirty-day mortality was lower in acute than in chronic hypernatremia but the difference was not significant (21% versus 41%, respectively; P=0.10).

Although there was a clear association between slow rates of correction and/or persistence of severe hypernatremia and mortality in this study and a similar study published several years ago (21), the reason for this association is not clear. In contrast to the previously published study, Alshayeb and coworkers excluded patients with low BP (systolic BP <90 mmHg) at the time of diagnosis of hypernatremia because these patients were more likely to receive fluid resuscitation with normal saline; low BP in the included patients did not contribute to the multivariable model of 30-day patient mortality. However, terminal underlying medical conditions as reflected by DNR status may have influenced physician behavior such that patients who were considered terminal may not have been vigorously rehydrated.

Regardless of what correction rate is chosen, attention must be paid to the patient’s volume status when treating hypernatremia. Although hypernatremia means intracellular dehydration, it does not necessarily mean extracellular dehydration. In many cases of hospital-acquired hypernatremia, water losses are replaced with isotonic saline, maintaining or, if sodium excretion is impaired, expanding the extracellular volume, causing clinically apparent edema (22). In such cases, as in patients with acute salt poisoning, administration of electrolyte-free water must be combined with efforts to eliminate excess salt, either with diuretics or dialysis.

**Brain Damage in Hypernatremia**

If the serum sodium concentration increases within minutes (as can occur after acute poisoning caused by salt ingestion or inadvertent intravenous infusion of hypertonic saline during therapeutic abortion), acute brain shrinkage causes intracerebral hemorrhage and, in most cases, a fatal outcome within hours. Furukawa et al. report a depressed woman who died of pulmonary edema and subarachnoid hemorrhage after ingesting 700 ml of soy sauce containing 75 g (1300 mEq) of sodium chloride (23).

Severe acute hypernatremia that is not quite as abrupt as that which occurs with acute salt ingestion or a bolus intravenous salt infusion can result in osmotic demyelination analogous to what is found after rapid correction of hyponatremia (6,24–25). In many reported cases, extrapontine lesions have involved the limbic system (27). Theoretically, lithium might predispose to such injury because, like hyponatremia, it reduces the concentration of the brain organic osmolyte, myoinositol (28), which is protective against osmotic demyelination (29).

Ismail et al. searched the literature and identified 30 patients with radiologic abnormalities associated with acute (>48 hours) hypernatremia (25). Osmotic demyelination syndrome was found in 80% of the patients: 16.7% with isolated central pontine myelinolysis (CPM), 33% with isolated extrapontine myelinolysis (EPM), and 30% with combined CPM and EPM.

**Figure 5-2.** Mean serum Na⁺ correction rate over time between the 30-day survivors and nonsurvivors. Reprinted with permission from Alshayeb HM, Showkat A, Babar F, Mangold T, Wall BM: Severe hypernatremia correction rate and mortality in hospitalized patients. *Am J Med Sci* 341: 356–360, 2011.
Hippocampal lesions were noted in one third of the patients with EPM. Clinical symptoms associated with these imaging findings were similar in spectrum to those reported after rapid correction of hyponatremia, ranging from subtle cognitive changes to severe brainstem dysfunction and death. Imaging findings in the remaining patients were equally divided between vascular changes (subdural hematoma, infarction, and dural sinus thrombosis) and volume changes (cerebral edema in 17% and brain shrinkage in 7%).

Not all cases of severe, acute hyponatremia result in brain damage. In one remarkable case, a 33-year-old woman survived without sequelae after her serum sodium concentration rose to 200 mEq/L during an 8-hour surgical procedure in which she received 3000 ml of hypertonic saline irrigation of multiple intraperitoneal cysts (30). Hyponatremia was recognized when she developed a major motor seizure postoperatively (treated with benzodiazepam) followed by agitation and hyperthermia to 39°C. Treatment with 2.5% dextrose in water at 200 ml/h combined with a furosemide drip lowered her serum sodium by 46 mEq/L (approximately 2 mEq/L per hour) within 24 hours.

References


Case 6: Diabetes and Acidosis

A 16-year-old woman has an 8-year history of type 1 diabetes mellitus that has been well controlled with an insulin pump. She recently developed a dental
emia is severe (and this is usually due to elevated appropriate testing is required. When the hyperlipidemia must be a strong consideration in this case and may contribute to the hyperlipidemia. Certainly pancreatitis may be precipitated by the hyperlipidemia. Conversely, the development of acute pancreatitis that this complication is precipitated by the hyperlipidemia. Certainly pancreatitis associated with acute pancreatitis and it is possible that this complication is precipitated by the hyperlipidemia. Conversely, the development of acute pancreatitis may contribute to the hyperlipidemia. Certainly pancreatitis must be a strong consideration in this case and appropriate testing is required. When the hyperlipidemia is severe (and this is usually due to elevated VLDL) the water phase of the serum may be reduced from its usual 93% to much lower levels. This will generate a “water displacement” artifact that will spuriously reduce the [Na] measurements carried out with any device that requires measurement of a quantitative volume of serum during the analysis. That includes the flame photometer and any device that utilizes indirect potentiometry. In contrast, a direct measurement of serum [Na] that does not require a specific volume of serum is not affected by this artifact. The currently utilized technique that accomplishes such measurements is direct potentiometry. Refer to Case 2 for a more complete discussion of these water displacement forms of pseudohyponatremia. However, with regard to this patient, pseudohyponatremia due to hyperlipidemia was appropriately considered and then ruled out by measurement of her [Na] with a bedside handheld device called an i-STAT. The i-STAT device our hospital utilizes measures [Na] with direct potentiometry. Therefore, measurements with this instrument are not subject to water displacement artifacts. The admission [Na] was similar to that reported by the central chemistry laboratory at 116 mEq/L (note most central/reference chemistry laboratories utilizes indirect potentiometry for [Na] measurement. If significant hyperlipidemia had been present, we would have expected a significantly higher [Na] value with the i-STAT). Thus, pseudohyponatremia was very appropriately considered in this patient but was not present. If it had been present, then the subsequent discussion would be based on the [Na] determination made with the i-STAT device or the [Na] corrected for hyperlipidemia as discussed in Case 2.

Pseudohyponatremia or Pseudonormonatremia

There is another interesting [Na] artifact that has been recognized as the differences between direct and indirect potentiometry have become better understood. That is the issue of pseudohyponatremia or pseudonormonatremia (in a patient with true hyponatremia). This artifact is caused by the opposite phenomenon as that responsible for water displacement causes of pseudohyponatremia. Just as displacement artifacts generate pseudohyponatremia when increased blood lipids and solids reduce the water phase of the serum or plasma from its normal 93% range, marked hypoproteinemia (and possibly hypolipidemia) will increase the water phase above 93%. Once again, direct analysis of the [Na] in the water phase by direct
potentiometry will be an accurate reflection of the true 
[Na] in the plasma or serum water, but any analytic
 technique that requires a quantitative volume of the
 specimen (i.e., indirect potentiometry or flame
 photometry) will result in a greater than normal volume of
 water and an artificial increase of the [Na] (2).
 Dimeski et al. recently compared direct and indirect
 potentiometry (ion-selective electrode) measurements
 of [Na] in 346 hospital clinical specimens and noted
 important differences (≥4 mEq/L) in 25% of the
 intensive care unit (ICU) specimens and 8% of hospital
 wide specimens (3). In the ICU, 97% of the patients
 with a difference of ≥4 mEq/L were due to low protein
 concentrations. Most of the hospital-wide differences
 of ≥4 mEq/L were also due to low protein concen-
 trations. Figure 6-1 shows the relationship between
 total protein concentration and the difference between
 the two [Na] measurements.

Note that many patients with the lowest protein
 concentrations had an artifactual increase in [Na] in
 the 6–9 mEq/L range. This would generate pseudohy-
 pernatremia in those with an actual normal [Na] and
 pseudonornonatremia in those with moderate degrees
 of true hyponatremia. These artifacts will have complex
 effects on the calculation of the AG (4,5). It is unclear
 how each variable would be affected, but clinically
 important effects may exist (2–4). In one recent study,
 low albumin levels had a much more dramatic effect on
 [Na] than on [Cl] (5). This may relate to differences in
 the way various factors affect the chemical activities of
different ions. Furthermore, hypoalbuminemia would
 also produce a true reduction of the AG (6,7). These
 issues also can become extremely important when the
 osmolality of serum or plasma is calculated in order to
determine whether an osmolar gap exists when the
 ingestion of various poisons or toxins are considered.

It is imperative that nephrologists understand
 how [Na] is measured at each of their hospitals and
 offices, which bedside or STAT devices are utilized,
 and the specific techniques that the various instruments
 utilize.

Hyperglycemia-Related Hyponatremia

Next we must consider the effect of the patient’s
marked hyperglycemia on her [Na].

In the late 1940s and early 1950s, Seldin et al.
published a series of papers that elegantly demonstrated
that high blood, and extracellular fluid (ECF), glucose
concentrations generated osmotic pressure across most
 cell membranes and thereby caused the transfer of
a large volume of water from the intracellular
 fluid (ICF) to the ECF (8–10). Hyperglycemia in these
studies was either due to poorly controlled diabetes or
was induced in normal subjects by the infusion of
concentrated glucose solution. As water shifted from
the ICF to expand the ECF volume the ECF sodium
concentration fell (because a fixed amount of sodium
salts were now dissolved in an expanded ECF space).
This reduction in [Na] was associated with increased
osmolality and a contraction of most intracellular fluid
spaces. This is in contrast to most other forms of
hyponatremia, which are associated with hypoosmo-
lality, hypotonicity (see below), and cell swelling. This
type of hyponatremia is called translocational hypona-
remia. In addition to hyperglycemia, it occurs with

\[ \text{Figure 6-1. A comparison of sodium concentration mea}-
\[ \text{ured with indirect and direct potentiometric instruments in}
\[ \text{patients with differing total plasma protein concentrations.}
\[ \text{Assume that the direct potentiometric sodium concentration is}
\[ \text{the “true” sodium measurement (reflecting the concentra-}
\[ \text{tion of sodium dissolved in plasma water) and that the}
\[ \text{indirect potentiometric measurements are subject to errors}
\[ \text{generated by either increased or decreased quantities of}
\[ \text{solids in the blood (primarily lipids and proteins) that}
\[ \text{generate a water displacement artifact. Then patients with}
\[ \text{high total plasma protein concentrations have reduced indi-}
\[ \text{rect sodium concentrations (i.e., pseudohyponatremia),}
\[ \text{whereas those with lower than normal total protein concen-}
\[ \text{trations have higher indirect sodium concentrations (i.e.,}
\[ \text{pseudohypernatremia) than the “true” sodium concentration}
\[ \text{measured with direct potentiometry. Reprinted with permis-}
\[ \text{sion from Dimeski G, Morgan TJ, Presneill JJ, Venkatesh B:}
\[ \text{Disagreement between ion selective electrode direct and}
\[ \text{indirect sodium measurements: Estimation of the problem in}
\[ \text{a tertiary referral hospital. J Crit Care 27: 326.e9–e16, 2012.} \]
mannitol infusion, as well as with sucrose infusion (associated with intravenous immunoglobulin [IG] treatment) when renal function is reduced (11). It also transiently exists when excessive glycine is infused during urologic (usually transurethral resection of the prostate TURP) or gynecologic procedures (12). Although this phenomenon is sometimes called pseudo-hyponatremia, such nomenclature is incorrect and confusing. The sodium concentration is in fact truly reduced—there is nothing artifactual or “pseudo” about the electrolyte measurement. However, as discussed, this form of hyponatremia is generally associated with an increased osmolality of body fluids and contraction of the ICF. Seldin et al. also demonstrated that resolution of the hyperglycemia essentially eliminated the additional glucose osmoles from the body water spaces and caused the translocated component of ECF water to move back into the ICF (8). This shift returns the [Na] to near its original level. Figure 6-2 shows the data from a normal subject whose glucose concentration was increased with the infusion of concentrated glucose solution and then returns to normal. The dotted line shows how the [Na] fell to 115 mEq/L and then returned to 133 mEq/L when the glucose infusion ceased.

In subsequent years, it was deemed important to calculate how much the [Na] should be expected to fall for any given degree of hyperglycemia in order to determine whether the [Na] that results after correction of the hyperglycemia would be in the normal range, reduced, or increased. If the posthyperglycemic “corrected [Na]” was determined to be low, this would then portend hypo-osmolal hyponatremia and an overhydrated state. If the posthyperglycemic “corrected [Na]” was determined to be high, this would portend hyperosmolal hypernatremia and a dehydrated state.

Although Seldin et al. did not calculate how much the [Na] should fall as [glucose] increased, or a [Na]/[glucose] ratio, one can calculate this number from the data such as that shown in Figure 6-2 and arrive at a ratio of a 1.74 mEq/L fall in [Na] for each 100 mg/dl increase in [glucose]. Despite these data, in the early 1950s, Dr. Louis Welt proposed a ratio of a 2.8 mEq/L fall in [Na] for each 100 mg/dl increase in [glucose] and a similar increase in [Na] should occur when the [glucose] fell by 100 mg/dl (13,14). Welt’s ratio calculation was empirically derived from the following facts and assumptions: 100 mg/dl of glucose represents about 5.6 mOsm/L (1000 mg/L /180 mg/mOsm = 5.6 mOsm/L). Two milliosmole of glucose are required to replace each milliequivalent of sodium because each sodium ion is accompanied by an anion, mainly chloride or bicarbonate, which also generates osmotic pressure. Therefore, the 5.6 mOsm/L is divided by 2 to yield 2.8 mOsm. Therefore, 2.8 mEq/L of Na can be replaced by 100 mg/dl of glucose and maintain osmolal equality. This is generally correct; however, the conclusion that a 2.8 mEq/L [Na] fall (or increase) will occur for each 100 mg/dl glucose rise (or fall) is also based on another assumption that is incorrect. The calculation assumes that the “addition” of glucose to the ECF will transiently raise the ECF osmolality and cause water to shift from the ICF to the ECF until the ECF osmolality has been returned to its baseline level. For the next quarter century, Welt’s sodium correction ratio of 2.8 mEq/L [Na] fall (or increase) was used by the vast majority of clinicians.

However, this analysis did not account for the fact that the addition of glucose osmoles to the body

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**Figure 6-2.** Glucose concentration was increased in a normal subject by infusing concentrated glucose solution intravenously. The solid line at the top of the graph shows the sum of the sodium concentration and glucose concentration divided by 2. (The glucose has been divided by 2 in order to make its osmotic effect similar sodium which is accompanied by and anion.) This parameter increased from 135 to approximately 140 mmol/L. (Also note this concentration in mM/L can be doubled in order to approximate the serum osmolality). The dotted line shows that the sodium concentration fell from its initial level (132 mEq/L) to approximately 115 mEq/L. After cessation of the glucose infusion, as the plasma glucose concentration fell, the sodium concentration simultaneously increased, returning to its original level. Also shown are the urinary excretion of sodium and potassium during this study. Modified from Seldin DW, Tarail R: Effect of hypertonic solutions on metabolism and excretion of electrolytes. *Am J Physiol* 159: 160–174, 1949.
fluids raises the total number of osmoles in the body or that a water shift from the ICF to the ECF will raise the ICF osmolality. Therefore, the final osmolality of the ECF (and ICF) at equilibrium must be significantly higher than the initial baseline osmolality. (Note that the Seldin et al. had clearly demonstrated that the equilibrium osmolality in the hyperglycemic patients and subjects was significantly increased above the baseline but that observation was ignored—see Figure 6-2.)

In 1973, Murray Katz published a very short (<1 page) paper in the New England Journal of Medicine that addressed the error described above (15). This paper was basically a “thought experiment” without any clinical or experimental data. It was based on the example of a 70 kg man whose total body water volume was 60% of his body weight with one third of the water in the ECF and two thirds in the ICF. Thus, total body water was 42 L, the ECF volume was 14 L, and the ICF was volume 28 L. The initial [Na] was 140 mEq/L and [glucose] was 100 mg/dl (or 5.6 mM/L). Thus, the initial osmolality was 2 × [Na] = 280 + 5.5 or about 285 mOsm/L. Then 1000 mOsm of glucose was added to the ECF, transiently raising the osmolality of this space. It was assumed that the glucose was an effective osmole that could not enter any intracellular space. Adding 1000 mOsm to a 14 L space would transiently raise its osmolality by approximately 71 mOsm/L. This increase in ECF osmolality would shift water from the ICF to the ECF, which will simultaneously reduce the ECF osmolality and increase the ICF osmolality.

The shift continues until a new equilibrium osmolality is achieved. The correction factor, or ratio, was calculated to be a 1.6 mEq/L fall (or rise) in the [Na] for each 100 mg/dl increase (or fall) in [glucose]. (Note that this is very close to the 1.74 ratio one can calculate from the Seldin et al. data.) For the next quarter century, a 1.6 mEq/L [Na] fall per 100 mg/dl [glucose] correction ratio was widely utilized. However, several reports suggested that there were also theoretical problems with this ratio and the assumptions upon which it was based.

In 1975, Roscoe et al. (16) reminded us that not all ICF spaces were insulin sensitive and that glucose may enter certain cells more or less freely. The brain, liver, kidneys, and lungs are relatively “insulin insensitive” tissues and to varying degrees may equilibrate with the hyperglycemic ECF by taking up glucose. Also in the case of the liver, its cells may manufacture much of the glucose. Therefore, these tissues may not participate in the water shift from the ICF to the ECF in the same fashion as muscle cells. On this basis, the authors calculated that the 1.6 mEq/L [Na] fall per 100 mg/dl [glucose] rise was too large and suggested that the correction ratio should be reduced to 1.35 mEq/L [Na] fall per 100 mg/dl [glucose] increase. Of greater importance than that rather small downward correction of the ratio was their observation that the development of hyperglycemic translocational hyponatremia could possibly shift water into brain cells and thereby contribute to cerebral edema. This could be especially important in children with diabetic ketoacidosis who are at increased risk for this not infrequently fatal complication (17).

**Diabetic Ketoacidosis and Cerebral Edema**

To understand how this occurs, one must understand the difference between effective osmoles, which generate a hydrostatic pressure or tonicity, and ineffective osmoles, which do not. If urea is added to the ECF, it raises osmolality but does not cause any water shifts (except very transiently if its serum concentration increases rapidly). This is due to the fact that urea rapidly penetrates cells so that its concentration quickly equilibrates between the ECF and ICF. Thus, urea does not cause a water shift and is therefore categorized as an ineffective osmole. Other ineffective osmoles are ethanol, other alcohols, and glycols. In contrast, effective osmoles are restricted to the ECF and if their concentration changes, osmolar equilibration requires a water shift. The osmolality generated by effective osmoles can also be called *tonicity* and the portion of a solution’s total osmolality composed of effective osmoles is the solution’s tonicity.

If glucose is an “effective” osmole for most tissues (such as muscle) but not for others, then with respect to the glucose permeable tissues, the effect of glucose *vis-a-vis* water movement would be similar to urea. Consequently, if hyperglycemia develops and causes a translocational fall in Na, but the glucose is not an effective osmole in certain tissues (*i.e.*, certain brain cells), then in those cells water will actually move from the ECF into the ICF and cause cell swelling rather than contraction. Such an effect may contribute to the cerebral edema which sometimes occurs very early in the course of pediatric diabetic ketoacidosis (DKA). In contrast, pediatric DKA-associated cerebral edema that occurs later in the course may be related to
excessive water administration and a fall in the glucose-corrected [Na] \( (18) \). Several groups have suggested that a too rapid fall in the effective osmolality, defined as \( 2 \times [\text{Na}] + \frac{[\text{glucose mg%}]}{18} \), may contribute to the development of cerebral edema \( (19,20) \).

Durward et al. studied 53 children with severe DKA (mean pH \( 6.92 \pm 0.08 \)) and identified 32 who developed cerebral edema (diagnosed using neurological status, response to osmotherapy, and neuroimaging) and 21 who did not (controls) \( (18) \). Those with cerebral edema were divided into an early developing group (within the first hour of presentation, \( n=15 \) patients) and late developing group (after the first hour but within 2 days, \( n=17 \) patients). Figure 6-3 shows prototypical trajectories of osmolality-based variables for these three groups. (Note that the serum glucose is measured in mm/l; to covert to mg%, multiple by 18. In addition, the [Na] correction factor used is the Katz 1.6 mEq/L [Na] fall (or increase) per 100 mg/dl [glucose] increase (or fall)).

The group of children with late developing cerebral edema generally had a fall in effective osmolality \( (2 \times [\text{Na}] + [\text{glucose}]/18) \) and the [Na] corrected for [glucose]. However, there is still no evidence that raising the [Na] to maintain effective osmolality as [glucose] falls is protective.

![Figure 6-3](image_url)

*Figure 6-3.* The prototypical trajectories of four parameters plotted against time during the first day of admission for 53 children with diabetic ketoacidosis. The four parameters are as follows: (1) effective osmolality (defined as \( 2 \times [\text{Na}] + [\text{glucose}] \) all measured in mmol/L), (2) serum glucose (mmol/L), (3) [Na] (mmol/L), and (4) glucose-corrected [Na] using \( \Delta [\text{Na}] / \Delta [\text{glucose}] \), which is equivalent to a 1.6 mEq/L sodium increase for each 100 mg/100 ml glucose decrease. The children were divided into three groups. The control group (21 patients) had no clinical evidence of cerebral edema. The early cerebral edema group (15 patients) had evidence of cerebral edema within 1 hour of presentation to the hospital (early does not refer to mild but instead refers to cerebral edema developing sometime before admission or within the first hour of hospitalization). The late edema group (17 patients) developed evidence of cerebral edema after the first hour after admission, but within the first 48 hours. Note that patients in all three groups had a similar pattern of fall in glucose concentrations. However, the late developing cerebral edema group had a more dramatic fall in both effective osmolality and corrected serum sodium concentration during the first day of admission. Therefore, although the glucose levels fell similarly in all of the groups, the increase in sodium concentration associated with that fall was much less in the group that developed late cerebral edema than in children who did not develop this complication. The corollary is that the corrected serum [Na] fell in this group. Reprinted with permission from Durward A, Ferguson LP, Taylor D, Murdoch IA, Tibby SM: The temporal relationship between glucose-corrected serum sodium and neurological status in severe diabetic ketoacidosis. *Arch Dis Child* 96: 50–57, 2011.
Pediatric cerebral edema continues to be the most feared complication of pediatric DKA with a high mortality and chronic morbidity rate. The exact contribution of intravenous fluid composition and infusion rate, metabolic acidosis, bicarbonate administration, and insulin therapy to this dreaded complication remains very uncertain and it is hoped that a new prospective trial will define the best therapeutic approach (21).

Hyperglycemia-Related Hyponatremia Continued

In 1985, Moran and Jamison pointed out several other problems with Katz’s assumptions (22). They observed that the glucose that is added to the ECF in most patients is not derived from exogenous sources but usually originates in the ICF (of liver cells) and that the generation of this glucose consumes other osmoles such as pyruvate, lactate, and glycogen. In addition, a more comprehensive mathematical analysis indicated that the ratio between the changes in [Na] and [glucose] could not be linear but would vary with the [glucose]. Lastly, they emphasized a critical point that should of course be obvious: all of these theoretical calculations assume that there is no net addition or removal of water and/or solute from the patient’s fluid spaces. Of course that is almost never the case. The patient who presents with severe hyperglycemia has almost always experienced a solute diuresis, is usually ingesting fluids, and/or is vomiting. Figure 6-4 from Moran et al. shows how the [Na]/[glucose] ratio will change as the ECF volume and glucose concentration changes. Relative ECF expansion will reduce the ratio, whereas contraction will increase the ratio. The ratio also falls as the glucose concentration increases.

What about real-life observations? Most of them, starting with the Seldin et al. data (8–10), support the 1.6 mEq/L [Na] fall per 100 mg/dl [glucose] correction ratio that Katz proposed. In 1981, Nanji also confirmed a correction ration of 1.6 mEq/L [Na] fall per 100 mg/dl [glucose] after adjusting for fluid and electrolyte balance in 10 patients with either diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome (23). In 1982, Tzamaloukas et al. reported that anuric dialysis patients who developed hyperglycemia and hyponatremia and were then corrected displayed a [Na]/[glucose] change ratio very similar to the Katz ratio of 1.6 mEq/L [Na] fall per 100 mg/dl [glucose] increase (24). However, two patients with marked anasarca and a relatively much larger than normal ECF had a change in [Na]/[glucose] slope that was <1.6. That is consistent with the data shown in Figure 6-4. In 1986, Tzamaloukas et al. reported data from a larger group of hyperglycemic hemodialysis and peritoneal dialysis patients. Although they again found the correction ratio to be 1.6 mEq/L [Na] fall per 100 mg/dl [glucose] in the...
peritoneal dialysis patients, they measured a larger ratio of 2.4 in the hemodialysis patients (25).

In 1999, Hillier et al. prospectively studied six healthy participants whose glucose concentration was acutely raised to >600 mg/dl over 1 hour by infusing somatostatin to block endogenous insulin secretion and then infusing 20% dextrose in half normal saline (26). After acute hyperglycemia (>600 mg%) had been achieved, the dextrose/half normal saline infusion was stopped and insulin was infused until the glucose had fallen to 140 mg/dl. Figure 6-5 shows the relationship between the rise in [glucose] and fall in [Na].

Figure 6-6 shows the [Na] as a function of plasma [glucose] analyzed as a simple linear relationship. The dotted line has a slope of 1.6 mEq [Na]/100 mg% [glucose] as suggested by Katz. The solid line, with a slope of 2.4/100 mEq [Na]/100 mg% [glucose], better fits the data. If the data is divided into two groups on the basis of [glucose], those with [glucose] <450 mg% and those with [glucose] >450 mg%, and regression lines are calculated for these two data groups then the slope of the relationship for the lower range of glucose levels is 1.6 mEq [Na]/100 mg% [glucose] identical to the values predicted by Katz. However, for glucose

Figure 6-5. Hyperglycemia was produced rapidly in six healthy participants by infusing 20% dextrose in half normal saline. Endogenous insulin had been suppressed with somatostatin infusion. Then the hyperglycemia rapidly resolved. The graph shows how [Na] fell as the [glucose] increased and later how [Na] increased as the [glucose] fell back toward normal. Reprinted with permission from Hillier TA, Abbott RD, Barrett EJ: Hyponatremia: Evaluating the correction factor for hyperglycemia. Am J Med 106: 399–403, 1999.

Figure 6-6. Hyperglycemia was produced rapidly in six healthy participants by infusing 20% dextrose in half normal saline. Endogenous insulin had been suppressed with somatostatin infusion. Then the hyperglycemia rapidly resolved. The graphs demonstrate the relationship between the serum [Na] measured as milliequivalents per liter and the [glucose] measured as milligrams per decaliter. (A) The upper panel shows that all of the data are analyzed for a single straight-line relationship. The result is the solid line with a slope of 0.024 (this represents a ΔPNa/ΔG of a 2.4 mEq sodium fall for each 100 mg/dl glucose increase). Also shown is a dotted straight line drawn with a slope of a 1.6 mEq/L sodium for each 100 mg/dl glucose increase as proposed by Katz in 1974. (B) The lower panel shows the same data divided into two groups: [glucose] <400 mg/dl and [glucose] >400 mg/dl. A straight-line relationship is calculated for each of these two groups. The milder hyperglycemic group (glucose <400 mg/dl) has a slope of 0.16, which indicates that the ΔPNa/ΔG is a 1.6 mEq/L fall in Na for each 100 ml increase in glucose. This is consistent with the Katz’s 1974 conclusion. However, the data points for glucose >400 mg/dl have a much steeper slope of 0.04. This indicates a ΔPNa/ΔG of 4.0 mEq/L fall in Na for each 100 ml increase in glucose. Reprinted with permission from Hillier TA, Abbott RD, Barrett EJ: Hyponatremia: Evaluating the correction factor for hyperglycemia. Am J Med 106: 399–403, 1999.
values >450 mg%, the slope is much steeper at 4.0 mEq [Na]/100 mg% [glucose]. As a compromise for bedside simplicity, Hillier et al. proposed that the ratio of 2.4 mEq [Na]/100 mg% [glucose] shown in Figure 6-6 be used across the entire glucose range. It is of interest to note that these findings are at odds with the theoretical calculations of Moran et al., discussed above, as shown in Figure 6-4. They predicted that the [Na]/[glucose] correction ratio should fall as the glucose concentration increases. Hillier et al. found the opposite result.

Additional clinical data about this relationship have been published since the report by Hillier et al. Penne et al. examined the relationship in 208 hemodialysis patients who had at least three monthly serum [sodium] and [glucose] measurements and were found to have a difference between the lowest and highest glucose value of >300 mg/dl. They determined that the data showed a ratio of 1.5 mEq/L [Na] fall/100 mg% [glucose] increase and concluded that the 1.6 mEq/L [Na]/100 mg% [glucose] proposed by Katz was acceptable for clinical practice (27).

Oh et al. analyzed data from 22 children (mean age 10.2 years) with DKA. They calculated the net fluid volume and electrolyte balance of these patients by analyzing the volume and composition of infused intravenous fluid and urine collection. After this correction for overall fluid and electrolyte balance, they calculated a ratio that was also very similar to Katz’s of between 1.5 and 1.8 mEq/L [Na]/100 mg% [glucose] (28).

So what [Na]/[glucose] correction ratio should we use? The most important point about the ratio is not the absolute number that is generated but the physiologic concepts that underpin the relationship. When an effective osmole such as glucose or mannitol is added to the ECF, the osmolality of this space increases and water must shift from the ICF to the ECF, expanding the ECF and contracting the ICF (with the exception of glucose permeable cells as discussed above). The shift continues until osmolar equilibrium develops. The [Na]/[glucose] change ratio will vary with the relative size of the two compartments and the absolute final concentration of the added substance. However, in clinical reality, things always become much more complicated because of varying degrees of fluid and solute ingestion and infusion, urine output and the electrolyte composition of the urine, plus the addition potential complications of diarrhea, vomiting, pre-existent edema or ascites, renal dysfunction, and so forth. Indeed, Halperin et al. most recently proposed that a [Na]/[glucose] ratio should not ever be calculated or used because of the many unknown variables that can alter the relationship (29). However, we still believe it is useful to calculate the expected or “glucose-corrected” Na so that the physician can gain a “ballpark” idea of the hydration status of the hyperglycemic patient. Of course, carefully following the electrolytes during the treatment period is of critical importance. As the [glucose] falls and [Na] rises, adjustments in fluid balance will probably be required. Whether one uses the Katz ratio value of 1.6 mEq [Na]/100 mg% [glucose] or the Hillier ratio value of 2.4 mEq [Na]/100 mg% [glucose] is less important than understanding the physiologic underpinnings of this relationship. For simplicity, we now use, and teach, a ratio of about 2.0 mEq [Na]/100 mg% [glucose] but always emphasize that this is a very rough approximation that will often require adjustment during the period of therapy.

Inherent in this calculation is an understanding that the effective osmolality will fall when the glucose has been returned to the normal range. It must be emphasized that some authorities believe that it is dangerous to allow this to occur and that interventions to maintain a stable effective osmolality are required (19,20). We await clinical data to determine whether they are correct.

**Ketone Testing**

The patient has an AG metabolic acidosis, her serum ketone test was positive, and she has marked hyperglycemia so a diagnosis of diabetic ketoacidosis is almost certain. There are two major organic acids that accumulate in the blood of patients with ketoacidosis: acetoacetic acid, which is a true ketoacid, and the reduced form of this acid, β-hydroxybutyric acid, which is actually a hydroxyacid. These two acids and the third “ketone body,” acetone (also a true ketone), which is formed by spontaneous decarboxylation of acetoacetic acid, are shown in the Figure 6-7. Until very recently, all of the tests for detecting ketone bodies in blood and urine were based on the nitroprusside (nitroferricyanide) reaction. The principle of these tests is that nitroprusside reacts with acetoacetate to form a bright purple complex. If glycine is added to the reaction, then both acetoacetate and acetone are detected, although the acetone reaction is much weaker (30,31). Nitroprusside powder, tablets (Acetest), or urine dipsticks (Ketostix) are usually utilized for this test (30,31). The nitroprusside tests are all semiquantitative.
under certain conditions. Whenever the NADH/NAH ratio is approximately 2 or 3 to 1. This ratio can increase from acetone, which is not an acid.

The urine test is graded on a scale of 1+ through 4+. The serum test is generally reported as the maximal dilution that still has a positive reaction (i.e., positivity at 1:2, 1:4, 1:8, and so forth). Although quantitative enzyme-based tests for the measurement of both acetoacetic acid and β-hydroxybutyrate have existed for some time, they were not widely available for rapid clinical purposes until quite recently.

It is important to understand that the nitroprusside reaction does not detect β-hydroxybutyrate. This can become a major issue because β-hydroxybutyrate is the dominant organic acid that accumulates in all forms of ketoacidosis. Under normal conditions, the total concentration of all three ketone bodies is <0.5 mM/L and the ratio of β-hydroxybutyrate to acetoacetate is approximately 2 or 3 to 1. This ratio can increase (i.e., acetoacetate shifts toward β-hydroxybutyrate) under certain conditions. Whenever the NADH/NAH+ ratio of hepatic mitochondria increases, the reaction is driven toward β-hydroxybutyrate and thus the β-hydroxybutyrate/acetoacetate ratio also increases (30–32). Marked acidemia also causes a similar shift. Two relatively common clinical disorders that shift the mitochondrial NADH/NAH+ ratio toward NADH and thus increase the proportion of β-hydroxybutyrate are alcoholic ketoacidosis and lactic acidosis (32). Lactate levels of >4 mEq/L are found in about 40% of patients with diabetic ketoacidosis who present to the emergency department (33). In these settings, the β-hydroxybutyrate may account for up to 90% of the accumulating ketoacid organic anions. When this occurs, the nitroprusside chemical reaction for “ketones” in both urine and blood will underestimate the severity of the ketoacidosis. Marked urine acidity also shifts the reaction toward β-hydroxybutyrate. Although it has been suggested that the sensitivity of the urine nitroprusside test can be improved by adding a few drops of hydrogen peroxide to a urine specimen and thereby nonenzymatically convert β-hydroxybutyrate to acetoacetate (34), several subsequent studies have not found this maneuver to be clinically useful (35,36). Another potential limitation is that a false positive urine ketone test may develop in patients treated with drugs such as captopril, penicillamine, and MESNA (2-mercaptoethane sulfonate Na), which contain free sulfhydryl groups that interact with the nitroprusside reagent.

These factors are the reason that alcoholic ketoacidosis or simultaneous ketoacidosis and lactic acidosis should be considered if the clinical circumstances are suggestive of these diagnoses, despite unimpressive urine and blood ketone tests. In addition, these interrelationships explain why nitroprusside ketone testing can become more positive despite overall clinical improvement when patients with simultaneous latic and ketoacidosis are treated. The bicarbonate levels may be improving and the AG may be closing but the ketone test becomes more positive due to an improved redox state and a NADH/NA+ ratio shift toward NAD+, which drives β-hydroxybutyrate toward acetoacetate.

Rapid enzyme-based clinical testing for ketones has recently begun to replace the nitroprusside methodology for analysis of blood ketones. This is a direct assay for whole blood, serum, or plasma β-hydroxybutyrate levels. Several β-hydroxybutyrate assay instruments are now commercially available and some are bedside “stat” devices (31,37,38). Use of such instruments should eliminate the potential errors related to the idiosyncrasies of the nitroprusside reaction. The normal concentration of β-hydroxybutyrate is 0.5 mm/L. It would be helpful to be able to compare the concentration of β-hydroxybutyrate with the increase of the AG. However, many of these assays cannot measure the actual β-hydroxybutyrate levels when they exceed 6 mm/L and those specimens are reported as >6 mm/L. The manufacturers advise against attempts to dilute the sample for reanalysis so a quantitative determination of
the severity of ketoacidosis cannot be carried out when severe ketoacidosis exists.

**Ketoacidosis and the AG**

When special efforts are made to quantitatively measure all of the organic acids that contribute to the various forms of metabolic acidosis (and the increment of the AG), a significant portion often remains unaccounted. This issue was discussed in the last edition of the *NephSAP* devoted to fluid, electrolyte, and acid-base disturbances (39–43). This issue is also true of diabetic ketoacidosis but a recent report helps shrink the unknown component of the AG in diabetic ketoacidosis. Lu et al. found that D-lactate levels are increased in patients with DKA (44). D-lactic acidosis, or at least a component of D-lactic acidosis, should now be considered in three clinical settings. First is the well recognized form of D-lactic acidosis associated with short gut syndromes, especially after ingestion of large carbohydrate loads (45,46). Second is a component of the AG metabolic acidosis associated with the accumulation of propylene glycol (47,48). This entity was also discussed in last edition of the *NephSAP* devoted to fluid, electrolyte, and acid-base disturbances (39) and the figure from that publication is reproduced here (Figure 6-8). Propylene glycol is a 3-carbon double alcohol that is metabolized to both D- and L-lactic acid. Because D-lactic acid is metabolized slowly, its levels can increase and generate an AG metabolic acidosis.

Now Lu et al. document relatively high D-lactic acid levels in patients with DKA. Figure 6-9 shows how both the glucose metabolite dihydroxyacetone phosphate and acetone can each be metabolized to D-lactic acid. The D-lactate levels averaged 3.8 mEq/L and some patients had levels in the 8–10 mEq/L range. These levels correlated nicely with the AG and with the reduction in [bicarbonate] (Figure 6-10).

The electrolytes of patient 6 were as follows: Na, 115 mEq/L; K, 3.4 mEq/L; Cl, 70 mEq/L; and HCO$_3^-$, 7 mEq/L. Her AG is calculated as:

$$\text{AG} = \text{Na} - (\text{Cl} + \text{HCO}_3^-) \text{ or } 115 - (70 + 7) = 38$$

Note, by convention we have used the [Na] uncorrected for the translocation of water produced by the hyperglycemia (glucose was 1100 mg%). This is done because expansion of the ECF caused by this water shift also dilutes the [Cl] and [HCO$_3^-$] by varying amounts in addition to [Na]. Consequently, the numbers as reported by the laboratory are plugged into the equation. However, if the [Na] had also been reduced

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Figure 6-8. The metabolic reactions leading from propylene glycol to form L-lactic, D-lactic acid, and methylglyoxal. Reprinted with permission from Sterns RH, Emmett M: Fluids, electrolyte, and acid-base disturbances. *NephSAP* 10: 91–193, 2011.

Figure 6-9. The metabolic steps resulting in the production of D-lactic acid in patients with diabetes mellitus. The glucose intermediate, dihydroxyacetone phosphate, and acetone derived from ketogenesis can each be converted to methylglyoxal. This compound can then be metabolized to D-lactate (also see Figure 6-8). Reprinted with permission from Lu J, Zello GA, Randell E, Adeli K, Krahn J, Meng QH: Closing the anion gap: Contribution of D-lactate to diabetic ketoacidosis. *Clin Chim Acta* 412: 286–291, 2011.
by a water displacement artifact such as hyperlipidemia (as discussed above), then the AG calculation would be more complicated. In that case, the [Na] after correction for hyperlipidemia should be used. However, if that situation exists, artifacts affecting the measurement of the [Cl] and [HCO₃] must also be considered and, if possible, corrected (see above). In the current case, this was not an issue.

**Ketoacidosis and Mixed Acid-Base Disorders**

The patient’s AG was very large at 38 mEq/L. If her baseline AG was 10 mEq/L, then the increment (or ∆) of the AG is 28 mEq/L. If her baseline [HCO₃] was 24 mEq/L, then its decrement (or ∆) is as follows: 24 – 7 = 17 mEq/L. Therefore, the AG has increased much more than the [HCO₃] has fallen. This large difference most likely represents another acid-base disorder – metabolic alkalosis. Either her [HCO₃] started much higher, at approximately 35 mEq/L, or HCO₃ was being generated during the acute illness. In either case, metabolic alkalosis can be diagnosed. She had a history of vomiting so the later mechanism is most likely. Although the average increase of the [AG] is generally similar to the fall in [HCO₃] in patients with DKA—that is, the ∆AG/∆[HCO₃] ratio is near 1, this ratio has a fairly wide range at the time of their admission. In the study of Adrogué et al. the average admission ∆AG/∆[HCO₃] ratio was 0.86 as shown in Figure 6-11 (49). This figure shows the ∆AG/∆[HCO₃] ratio in 150 DKA admissions. The patients whose ratio was <1 had a hyperchloremic component to their metabolic acidosis, or if the AG was not elevated at all then they had a pure hyperchloremic metabolic acidosis. Hyperchloremia develops in patients with DKA when renal function is relatively well preserved with a high GFR that permits the excretion of the organic acid anions (acetoacetate, β-hydroxybutyrate, and perhaps D-lactate, see Figure 6-9) as sodium and potassium salts. It becomes more and more dominant during the treatment phase of DKA when aggressive intravenous expansion improves the GFR and enhances organic acid anion excretion—a hyperchloremic component almost develops during the first day of treatment. In contrast, patients admitted with a ∆AG/∆[HCO₃] ratio much greater than 1, usually have coexisting metabolic alkalosis as described above. Studies by Paulson and Gadallah suggest that the difference between the ∆AG and the ∆[HCO₃] should be ≥8 mEq/L before a clinically important complicating acid-base disturbance is considered (50).

Sometimes the metabolic alkalosis is so severe that its magnitude exceeds the AG metabolic acidosis and the patient manifests alkalemia despite the existence of ketoacidosis. Lim called this entity diabetic
ketoalkalosis (51). This condition continues to be reported (52–54).

References


37. Klocker AA, Phelan H, Twigg SM, Craig ME: Blood 


Case 7: Negative Anion Gap

Mr. R.E. is a 74-year-old man who developed generalized weakness when he was 68 years old. Work-up at that time led to a diagnosis of myasthenia gravis. A thymoma was not seen on a computed tomography scan. He was begun on pyridostigmine (Mestinon) with marked symptomatic improvement. Recently, however, his condition deteriorated and he became much weaker. He also developed bilateral ptosis, difficulty swallowing his secretions, and dyspnea. He was admitted to the hospital for further evaluation and treatment. Soon after admission, his respiratory distress required emergent endotracheal intubation.

Past medical history includes adult onset diabetes mellitus. His only medications on admission were pyridostigmine 180 mg four times a day and Glucotrol 10 mg daily.

On initial examination his BP was 130/80 and his heart rate was 80 beats per minute and regular. He was afebrile. He had bilateral lid ptosis, bilateral sixth nerve palsy, and a markedly decreased gag reflex. He did have symmetrical diffuse muscle weakness. Reflexes were 1+ and symmetrical throughout.

The diagnosis established soon after admission was myasthenic crisis. Daily plasmapheresis (× 6 days) was initiated and the patient improved.

The renal service was asked to explain unusual electrolyte results. The patient’s admission chemistries included the following:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>135 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.1 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>122 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>20 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.2 mg/dl</td>
</tr>
</tbody>
</table>

Which ONE of the following is the MOST likely explanation for these chemistries?

A. Bromism
B. Salicylism
C. Multiple myeloma
D. Hypercalcemia
Discussion

This patient has chronic bromism (answer A) as a result of the long-term use of pyridostigmine bromide for treatment of his myasthenia gravis. Currently, pyridostigmine bromide (Mestinon) is the most commonly used drug in the United States with the potential to generate clinically significant bromide levels. There are several other bromide salt prescription drugs available in the United States but they are rarely used in quantities and long enough duration that they result in significant bromide accumulation. These drugs include dextromethorphan hydrobromide, halothane, neostigmine, pancuronium, propantheline, and scopolamine. One case of bromidism due to dextromethorphan has been published (1).

The widespread medical use of bromide dates back to the mid-19th century. Within a few years of its discovery as an element (1825–1826), bromide salts were introduced into clinical medicine and by the 1850s were being used for seizure prophylaxis and control. At that time, it was believed that the cause of epilepsy in many girls and women was related to repressed sexual desire and tension. Thus, “hysterical epilepsy” was a frequent diagnosis in the mid to late 19th century. (Note the entity of catamenial epilepsy is in fact a seizure disorder in which menstrual cycle hormonal variations are associated with seizure severity.) It had been noted that bromide salts produced sedation and also reversible impotence in men (2). Therefore, in 1857, bromide salts were introduced for the prevention of “hysterical seizures” and soon thereafter their use was extended to seizures generally (2,3). By 1900, sodium and potassium bromide salts had become one of the most widely utilized sedatives and anticonvulsants (4,5). It is interesting to note that the first edition of Goodman and Gillman’s landmark Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, published in 1941, devoted 11 pages of text to the therapeutic use of bromide salts (6). These salts were also the most important active ingredient of many extremely popular over-the-counter medications including “Bromo Seltzer” and “Mile’s Nerve.” The word bromide became part of common English vernacular as a substance or verbal comment that would “settle things down.” Unfortunately, many individuals developed dependence on bromide-containing medications and chronic bromide intoxication, or bromism, ensued. Chronic high bromide levels lead to confusion, disorientation, delirium, and hallucinations as well as several characteristic skin eruptions such as a pustular acne-like rash and granulomatous, purulent lesions called bromoderma. Evelyn Waugh’s novel The Ordeal of Gilbert Pinfold. A Conversation Piece is a semi-autobiographical description of the author’s personal struggles with chronic use and dependence on bromide salts (7).

Bromide distributes in body fluids almost exactly like the major physiologic halide, chloride (i.e., within the “chloride space”), and is transported by most anion exchangers and channels in a fashion very similar to chloride. However, slight differences in these distribution spaces and ion transport characteristics have long-term effects. When ingested chronically, the serum bromide level slowly increases and partially replaces some of the chloride in the extracellular fluid (4,8,9).

Figure 7-1 shows how bromide ingestion affects electrolytes, chloride concentration, and the anion gap. Assume that a normal individual has a serum [Cl] of 100 mEq/L and chronically ingests sodium and/or potassium bromide so that over time the bromide replaces 5 mEq/L of chloride in his extracellular fluid. His true [Cl] is then 95 mEq/L, his true [Br] is 5 mEq/L, and his true [total halide] is unchanged at 100 mEq/L. This is shown in the middle panel of the figure. If the true [Cl] could be measured, then the anion gap would have increased by 5 mEq/L [140 – (26+95) = 19]. If the true [total halide] were measured and this number was used instead of [Cl], then the anion gap would remain unchanged at 14 mEq/L. However, bromide will usually alter the measurement of chloride so that pseudohyperchloremia or artifactual hyperchloremia develops. This occurs because bromide reacts very similarly to, but more strongly than, chloride when chloride is measured with most clinical analytical instruments. Therefore, each bromide ion may register as 2–5 chloride ions (4,10,11). This artifact occurs with many colormetric and both direct and indirect ion-selective electrode chloride analyzers. In the example shown in Figure 7-1, in the right panel, the patient’s “chloride” concentration is reported as 120 mEq/L instead of its true level of 95 or the true halide concentration of 100. In this example, the result is an anion gap of −6 mEq/L. In some cases the [Br] exceeds 40 mEq/L and then generates apparent chloride concentrations of 225 mEq/L or more (11). This severe
The degree of pseudohyperchloremia will reduce the anion gap into the extreme negative range. If bromism is suspected, then the true total halide concentration as well as the true chloride and bromide concentrations can be accurately measured with certain coulometric instruments that utilize silver ion precipitation and oxidation-reduction reactions to accurately measure the chloride and bromide concentrations (10,11).

Bromism has largely disappeared as a clinical entity in the United States because virtually all bromide-containing medications have been removed from both over-the-counter and prescription drugs. However, an occasional case is still encountered. Bromide salts are still an important third-line agent for control of otherwise refractory seizure disorders and may actually be the very best anticonvulsant for certain pediatric neurologic conditions (12). Bromide-containing sedatives are still available in many countries other than the United States; therefore, cases of bromism continue to be reported globally and sometimes in the United States when these drugs are brought in from overseas (13,14).

The patient described above developed bromism as a result of the chronic use of the cholinesterase inhibitor pyridostigmine (Mestinon). This drug is widely used in the United States, primarily to treat myasthenia gravis. It is produced as a bromide salt and its use may lead to bromism, pseudohyperchloremia, and a negative anion gap (15,16). Another very unusual source of bromide is ingestion of citrus-flavored carbonated sodas. Many of these drinks use brominated vegetable oils to keep the citrus flavoring dissolved in the solution. If one ingests very large quantities of such sodas over a long period of time, then bromism may develop (17). Other halides such as iodine can also generate pseudohyperchloremia through similar mechanisms (18,19).

Another cause of pseudohyperchloremia has been described over the past few years. High salicylate levels can interfere with chloride measurements with certain chloride sensing ion-selective electrodes. These electrodes utilize a membrane that is specifically permeable to chloride. The difference in chloride concentration between the serum sample and a reference chloride solution generates an electrical potential difference that is proportional to the serum’s chloride concentration. High salicylate levels can alter the permeability characteristics of these membranes and increase their permeability to chloride. This results in pseudohyperchloremia (20–22). This is a reproducible artifact, but it has one very unusual characteristic related to the age of the measuring electrode. Chloride-specific membranes are designed to be used for several months before they are replaced. When the electrodes are “fresh,” the effect of salicylate is relatively small and marked pseudohyperchloremia does not develop. As the membranes age, the salicylate-induced artifact becomes more and more severe (20).

Another potential cause of pseudohyperchloremia is marked hyperlipemia. Some chloride assays are colorimetric assays and the light scattering effect of high plasma lipids create artifactual chloride elevations (23).
Table 7-1. Causes of a low or negative anion gap

1. True reduction of “unmeasured anion” concentration
   - Low albumin concentration (anion gap is not negative)
2. True elevation of “unmeasured cation” concentration
   (as chloride salts)
   - Anionic proteins, usually monoclonal IgG
   - Lithium, calcium, magnesium
3. Artifactual reduction of sodium with relatively accurate chloride and bicarbonate measurements
   - Water displacement errors:
     - Hyperlipemia; lipoprotein X
   - Inaccurate quantitative aspiration
   - Hyperviscosity
   - Abnormal precipitation
   - Monoclonal proteins
4. Artifactual hyperchloremia
   - Bromism
   - Aspirin poisoning
   - Hyperlipemia
5. Artifactual hyperbicarbonatemia
   - Monoclonal proteins

Table 7-1 lists other causes of a reduced or negative anion gap.

References

Case 8: Hyperchloremia

A 50-year-old Caucasian man was brought to the emergency department when he was found to be confused and wandering in the street. No other history was available. He was tachypneic and tachycardic. His temperature was 100°F. An examination revealed bilateral diffuse crackles and rhonchi and a chest X-ray showed diffuse bilateral infiltrates. He had the laboratory studies shown in Table 8-1. He was poorly responsive and emergently intubated for airway protection.

Table 8-1. Case 8: Patient laboratory studies

<table>
<thead>
<tr>
<th>Laboratory Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>133 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>186 mEq/L</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>10</td>
</tr>
<tr>
<td>BUN</td>
<td>33 mg/100ml</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.2 mg/100ml</td>
</tr>
<tr>
<td>Anion gap</td>
<td>- 63</td>
</tr>
<tr>
<td>ASA level</td>
<td>69.7 mg/100ml</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.0 gm/100ml</td>
</tr>
<tr>
<td>ABG (preintubation)</td>
<td>pH 7.43</td>
</tr>
<tr>
<td></td>
<td>pCO₂ 14 mmHg</td>
</tr>
<tr>
<td></td>
<td>HCO₃⁻ 9 mEq/L</td>
</tr>
</tbody>
</table>
A multilobar pneumonia was suspected (bilateral infiltrates, hypoxia, low-grade fevers, and leukocytosis with left shift). Broad-spectrum antibiotics were initiated and the patient was admitted to the intensive care unit (ICU). Soon after he arrived in the ICU, he suffered a cardiac arrest and could not be resuscitated. You arrived at his bedside during the attempt to resuscitate him.

After you reviewed his admission laboratory studies, you noted his severe hyperchloremia and negative anion gap and asked the laboratory to check his blood for bromide and salicylate. The results of the salicylate level retumed after he had been pronounced dead and was markedly elevated.

Several questions are raised by this patient and his very rapid demise. What was the cause of his bilateral pulmonary infiltrates? Could the endotracheal intubation and artificial ventilation have accelerated his clinical decline? If you had been called sooner, would emergency hemodialysis have saved his life?

Discussion

The occasional artifactual pseudohyperchloremia that occurs when the [Cl] is assayed in blood with high salicylate levels is an instrument dependant phenomenon described in the preceding paragraphs. When it occurs, it can be a clue to the diagnosis of otherwise occult salicylate poisoning. However, other than being a clue to the diagnosis, it does not directly affect the patient’s medical status or treatment. We will next review several relatively new aspects of salicylate poisoning and its treatment as they relate to this patient.

What was the patient’s pulmonary pathology? The initial diagnosis in the emergency department was diffuse bilateral pneumonia. This may have been the correct diagnosis but it is more likely that the infiltrates were due to salicylate-induced pulmonary edema. Although this entity has been recognized for many years and was well described in 1959 by Winters et al. (this is the same Robert W. Winters for whom the acidosis compensation equation is named), its pathogenic mechanism remains unclear (1). Glisson et al. recently reviewed the literature and summarized what is known about the diagnosis and treatment of this entity (2). This is a form of noncardiogenic pulmonary edema and it is believed that alterations in prostaglandin metabolism within the pulmonary parenchyma and increased vascular permeability are likely to exist but very little experimental data regarding pathogenesis have been published. Salicylate-related pulmonary edema is probably more common with chronic forms of salicylate toxicity but can certainly also occur with acute overdoses. There is also little definitive information about optimal treatment of this disorder. However, it is clear that this complication makes attempts to utilize aggressive volume expansion with sodium bicarbonate solutions very difficult. Patients with severe salicylate-induced pulmonary edema should probably receive emergency hemodialysis. More about dialysis is discussed below.

This patient was intubated emergently for salicylate toxicity and this intervention may have been necessary to protect his airway. However, it must be emphasized that intubation and mechanical ventilation can be disastrous for patients with salicylate poisoning and the intervention may have contributed to this patient’s demise. The reason relates to the issue of nonionic diffusion.

The principle of nonionic diffusion affects the urinary excretion of the drug and its compartmental localization and is especially important in relation to the toxicity and treatment of salicylic acid and its congeners. This important physiologic principle was well described in the 1940s and in 1958 was extensively reviewed by Milne et al. in the American Journal of Medicine (3). Salicylate is an acid with a pK of about 3.1. Therefore, at a pH of 7.4, 99.9995% of the drug is ionized as S⁻ and only 0.005% is in the undissociated HS form (Figure 8-1).

Changes of pH in the physiologic range will initially have almost no effect on the ionized fraction but will markedly change the concentration of the undissociated form HA. For example, a 0.3 unit change in pH will double (if the pH falls from 7.4 to 7.1) or halve (if the pH increases from 7.4 to 7.7) the HS concentration (Figure 8-2).

If at a blood pH of 7.4, the total salicylate concentration [SA] is 100 mg%, then the ionized [S⁻] have been published. Salicylate-related pulmonary edema is probably more common with chronic forms of salicylate toxicity but can certainly also occur with acute overdoses. There is also little definitive information about optimal treatment of this disorder. However, it is clear that this complication makes attempts to utilize aggressive volume expansion with sodium bicarbonate solutions very difficult. Patients with severe salicylate-induced pulmonary edema should probably receive emergency hemodialysis. More about dialysis is discussed below.

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If at a blood pH of 7.4, the total salicylate concentration [SA] is 100 mg%, then the ionized [S⁻]
concentration will be 99.995 mg% and the [HS] concentration will be 0.005 mg%. If the blood pH falls to 7.1, the $[S^-]$ concentration hardly changes, falling to 99.99 mg%, but the HA concentration doubles to 0.01 mg%.

The effect of this doubling of [HS] in the extracellular fluid (ECF) is profound because it is this moiety that most readily penetrates cell membranes. Assume that the nondissociated HS is in equilibrium across most cell membranes with its concentration in the intracellular water space. The total concentration of salicylate within the intracellular compartment will be different than the blood salicylate concentration. This is a result of more acid intracellular pH. The pH with cells varies in different tissues and intracellular compartments, but assume it is about 7.0. Use the example of a blood total salicylate level of 100 mg% with $[HS] = 99.995 \text{ mg}\%$ and $[S^-] = 0.005 \text{ mg}\%$ at pH 7.4. If the permeable HS equilibrates across the membrane and is also 0.005 mg% within the cell water space then the $[S^-]$ within the cell can be calculated to be equal to 40 mg%. If the blood pH falls to 7.1 and the ECF level of HS doubles to .01, a very large gradient for HS to flow from the ECF into the intracellular space is created. If the intracellular space [HS] equilibrates with the ECF [HS], the new intracellular [TS] will also double to approximately 80 mg%. Furthermore, as salicylate flows from the ECF into the intracellular fluid, the blood level will quickly fall.

Three figures from the important work of John B. Hill nicely demonstrate this phenomenon (4,5) (Figures 8-3 to 8-5). The first is a rat study that shows the salicylate levels in blood and various tissues after a fatal dose has been administered. Note that despite widely ranging blood levels, all the animals had brain salicylate levels between 35 and 55 mg/100 g tissue when they died. It is the tissue level of salicylate, especially brain levels that seem to correlate with fatality. The second is a dog study that shows how acute respiratory acidosis causes a sudden and dramatic reduction in blood salicylate levels and then how these levels rebound when the acidosis is reversed. The fall and rise in salicylate levels are caused by their translocation into the intracellular fluid of cells and then their return to the ECF on the basis of nonionic diffusion discussed above. Figure 8-3 shows the plasma and tissue levels of salicylate when the plasma pH is increased with NaHCO$_3$ or reduced with CO$_2$ inhalation in a rat experiment. Note especially the reduction and increase in brain salicylate concentrations with these maneuvers.

These principles have recently been highlighted by clinical reports that endotracheal intubation and

![Figure 8-2](image-url) The dissociation of salicylic acid to salicylate and a proton is displayed. When dissolved in a solution with a pH of 7.1, salicylic acid is almost entirely dissociated. The tiny fraction of unionized salicylic acid is 0.001% of the total concentration of salicylic acid plus salicylate. Although this concentration of unionized salicylic acid is still very low, it is double the concentration that would exist at a pH of 7.4.

![Figure 8-3](image-url) Rats were given a spectrum of lethal doses of salicylate via different routes of administration. All of the animals seized before death. The diagram demonstrates postmortem blood and tissue salicylic levels obtained from the animals immediately after death. The two dotted horizontal lines encompass all of the brain salicylate levels. It can be seen that the brain salicylate levels were all between 35 and 55 mg/100 g tissue at the time of death. In contrast, blood salicylate levels at the time of death had a much wider range that varied with the dose, route of administration, time required for the individual animal to die, the quantity initially infused, and the pH status. Reprinted with permission from Hill JB: Salicylate intoxication. N Engl J Med 288: 1110–1113, 1973.
mechanical ventilation may have catastrophic consequences in salicylate-poisoned patients (6,7). The respiratory alkalosis, which is usually very evident in older children and most adults with salicylate poisoning, is most likely protective and anything that impairs or reverses this response and causes the blood pH to fall may have severe adverse effects. Stolbach et al. (7) retrospectively reviewed the New York City Poison Control Center database over a 7-year period and identified seven patients with salicylate poisoning who were intubated and mechanically ventilated. Two died and one suffered severe neurologic injury. Although it is likely that these were very ill patients and some may have had a multidrug ingestion, intubation and artificial ventilation may have contributed to their poor outcome. After intubation some patients may continue to hyperventilate and "overdrive" their mechanical ventilator settings. However, sedation and muscle paralysis is often required during and after intubation and it may be impossible to adjust the ventilator settings to maintain the pCO₂ as low as necessary without producing hypotension. On the other hand, many adults with salicylate poisoning, especially when taken as a suicidal attempt, also ingest other drugs, toxins, and alcohol. Gabow et al. (8) found that approximately one third of adults with salicylate poisoning had taken other drugs, usually central nervous system (CNS) depressants, which often caused respiratory depression and respiratory acidosis. Thisted et al. reported on 177 consecutive patients with severe

Figure 8-4. The experiment shows the effect of acute acid-base disorders on blood salicylate levels in an anesthetized dog (phenobarbital). After being placed on a ventilator, a large dose of salicylate (232 mg/kg) was infused intravenously. When the inhaled gas mixture was switched from room air to an 80% oxygen and 20% CO₂ gas mixture, this generates acute respiratory acidosis and the arterial blood pH falls from 7.4 to 6.85. Note that the blood salicylate levels fall in parallel with the reduction in atrial blood pH. The gas mixture was then switched back to room air and the pH recovered to the normal range and the blood salicylate levels acutely increased. Although not directly measured in this experiment, a series of corollary experiments demonstrated that the reversible fall in salicylate levels was due to an intracellular shift of the drug. Then, when the acute respiratory acidosis was reversed, the salicylate moved back from the intracellular space into the ECF and the blood levels returned toward their prior levels. The blood concentrations of phenobarbital, also an acid with a pK = 7.1, changes in the same direction. Reprinted with permission from Hill JB: Salicylate intoxication. N Engl J Med 288: 1110–1113, 1973.

Figure 8-5. The distribution of salicylate as influenced by blood pH changes induced by a bicarbonate infusion and carbon monoxide inhalation in rats with intact kidneys. The bars represent the mean and the vertical lines ± one SEM. When the plasma pH is acidified, the salicylate moves into tissues and when it is alkalinized it moves out of tissues. However, note that the plasma salicylate level falls with acute metabolic alkalosis despite the movement of the drug out of tissues into the blood. This is due to enhanced renal excretion of salicylate when sodium bicarbonate is administered and the urine pH is alkalinized. Reprinted with permission from Hill JB: Experimental salicylate poisoning: Observations on the effects of altering blood pH on tissue and plasma salicylate concentrations. Pediatrics 47: 658–665, 1971.
salicylate poisoning admitted to a medical ICU (9). Almost half had respiratory failure and 27 of 177 patients died. The take-home message is to consider intubation a last resort in the salicylate-poisoned patient especially if the patient is hyperventilating and maintaining a low pCO₂ tension. On the other hand, rapid intubation is indicated when CNS depression has caused respiratory failure and a normal or high pCO₂.

Lastly, the issue of urine alkalinization and hemodialysis for salicylate poisoning has been addressed over the past few years. There is no doubt that alkalinizing the urine can effectively remove salicylate from the body. The underlying physiologic principle is again nonionic diffusion. A urine pH of 8 will initially reduced the concentration of HS to approximately 25% of its level in the blood. The resulting gradient will enhance movement of salicylate into the urine. Although other mechanisms, such as effects on specific transport proteins, may also play a role there is excellent experiment animal and human data to show that this maneuver works. Increasing the urine pH from 7 to 8 more than doubles the salicylate clearance (10). In a position paper by Proudfoot et al. (11), the authors state the following: “Based on volunteer and clinical studies, urine alkalinization should be considered as first line treatment for patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis.” They emphasize that the key point is urine alkalinization to a pH between 7.5 and 8.5 and that this is more important than the urine flow rate. They recommend that adults be given 225 mmol of sodium bicarbonate (equivalent to 225 ml of an 8.4% NaHCO₃ solution or 4–5 amps of hypertonic NaHCO₃) intravenously over about 1 hour. The loading dose can be accelerated and increased if acidemia exists. Monitor urine pH every 15–30 min until it is between 7.5 and 8.5, and then check urine pH hourly. The plasma potassium should also be checked hourly and replaced when hypokalemia develops. Plasma salicylate concentrations are checked hourly. The patient’s volume status must of course be monitored as well. Additional boluses of intravenous NaHCO₃ or a NaHCO₃ infusion can be used to maintain urine pH between 7.5 and 8.5. The alkalinization can be discontinued when plasma salicylate concentrations fall below 35 mg/dl.

Dialysis is an effective means of rapidly reducing salicylate levels. Salicylate, at therapeutic concentrations, has a volume of distribution that is smaller than the ECF at about 0.2 L/kg. This is due to the fact that it is 80%–90% bound by plasma proteins. However, when salicylate concentration increases to toxic levels, protein binding becomes saturated and the volume of distribution increases. Salicylate is a relatively small molecule (138 Da) and is readily dialyzed. This is especially true when the levels are high because a greater fraction is not protein bound. Fertel et al. believe that hemodialysis has been underutilized in many cases of salicylate poisoning and should be instituted more commonly and earlier (12,13). This point was previously made by Chapman and Proudfoot (14). Hemodialysis is probably indicated regardless of the patient’s clinical status when the salicylate levels are extremely high (e.g., >100 mg/dl). However, it is also indicated when the levels are lower but the patient has reduced renal function or is exhibiting clinical manifestations such as overt CNS toxicity or pulmonary edema.

Too much reliance on salicylate blood levels alone must be avoided. First, as discussed above, they may not reflect the more important tissue burden (especially within the brain) of the drug. Second, they may rise rapidly from very low levels as a result of delayed absorption from the gastrointestinal tract. Fatal cases of salicylate toxicity despite low or even absent initial levels continue to be reported (15–17).

When hemodialysis is instituted, Fertel et al. recommend a 3.5- to 4-hour treatment with blood flow rates of 350–400 ml/min using large surface area biocompatible hemodialysis membranes (12,13).

References


Nephrology Self-Assessment Program

Examination Questions

Original Release Date
July 2013

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June 30, 2015

Examination Available Online
On or before Wednesday, July 10, 2013

Audio Files Available
No audio files for this issue.

Answers with Explanations
- Provided with a passing score after the first and/or after the second attempt
- July 2015: posted on the ASN website in when the issue is archived.

Target Audience
- Nephrology certification and recertification candidates
- Practicing nephrologists
- Internists

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- Each participant is allowed two attempts to pass the examination (>75% correct) for CME credit.
- Upon completion, review your score and incorrect answers and print your certificate.
- Answers and explanations are provided with a passing score or after the second attempt.

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Instructions to obtain American Board of Internal Medicine (ABIM) Maintenance of Certification (MOC) Points
Each issue of NephSAP provides 10 MOC points. Respondents must meet the following criteria:
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- Below your score select “Click here to post to ABIM.”

MOC points will be applied to only those ABIM candidates who have enrolled in the MOC program. It is your responsibility to complete the ABIM MOC enrollment process.
1. A 69-year-old woman with diabetes, hypertension, and ESRD who was on hemodialysis presented to the emergency department having missed dialysis due to weakness. Upon arrival, she had a finger-stick glucose level of 38 mg/dl. Her physical examination showed an oral temperature of 36.2°C (97.1°F), BP of 151/85 mmHg, heart rate of 100 beats per minute, respiration rate of 32 breaths per minute, and 100% oxygen saturation. She appeared as an ill, elderly woman with a Kussmaul respiratory pattern, dry mucous membranes, and diffuse rhonchi in her chest. Her abdomen was soft with mild tenderness, and she was confused and weak. Fifty milliliters of a 50% dextrose solution was administered, and her mental status improved. Her laboratory results were as follows: sodium, 140 mEq/L; potassium, 6.7 mEq/L; chloride, 88 mEq/L; bicarbonate, 14 mEq/L; BUN, 40 mg/dl; and creatinine, 10.9 mg/dl. Arterial blood gas (ABG) on 6 L oxygen showed pH 7.37, pCO2 of 20 mmHg, and pO2 of 171 mmHg. Her serum lactate was 18.9 mmol/L. She improved rapidly with hemodialysis. Her medications included amiodarone, clonidine, gabapentin, glyburide/metformin, atorvastatin, lisinopril, and omeprazole.

Which ONE of the following is the MOST likely cause of her acid-base disorder?

A. Amiodarone toxicity
B. Metformin toxicity
C. Sepsis
D. Pyroglutamic acid metabolic acidosis

2. A 56-year-old man was found to have hypernatremia (serum sodium 149 mEq/L) on an outpatient visit to his oncologist. The patient had been treated for lung cancer with surgery and radiotherapy but the tumor had recurred in his right lung. His physical examination showed BP of 145/85 mmHg, pulse rate of 80 beats per minute, and respiration rate of 18 breaths per minute. There was dullness to percussion and reduced breath sounds over the entire right chest. His laboratory results were as follows: sodium, 150 mEq/L; potassium, 3.7 mEq/L; chloride, 119.0 mEq/L; bicarbonate, 24.0 mEq/L; creatinine, 1.9 mg/dl; BUN, 22.0 mg/dl; glucose, 130 mg/dl; and calcium, 12.1 mg/dl. His urinalysis showed osmolality of 230 mmol/kg and urine calcium of 460 mg/24 h.

The MOST likely mechanism contributing to this patient’s hypernatremia is which ONE of the following?

A. Reduced antidiuretic hormone (ADH) secretion
B. High luminal calcium antagonizing aquaporin 2 translocation to the apical plasma membrane
C. Serum calcium antagonizing aquaporin 2 translocation to the apical plasma membrane
D. Hypercalcemia induced increased solute excretion

3. A 22-year-old man with a history of short bowel syndrome due to a gunshot wound to his abdomen 5 years ago now presents to the emergency department complaining of confusion and weakness. He is taking no medications. His physical examination shows a thin man but not malnourished, with a BP of 110/80 mmHg, respiration rate of 15 breaths per minute, and heart rate of 82 beats per minute. He is afebrile. He has a large abdominal surgical scar. He is confused but without focal neurologic signs. His laboratory results are as follows: pH 7.29; PO2, 133 mmHg; PCO2, 29 mmHg; and HCO3, 14 mEq/L.
lactate level is 2 mmol/L and his β-hydroxy butyrate is 1 mmol/L. His results are negative for ethanol, methanol, and ethylene glycol.

**Which ONE of the following should be done to treat his metabolic acidosis?**

A. Oral antibiotic therapy  
B. Intravenous infusion of Ringer’s lactate  
C. Acute hemodialysis  
D. Administration of fomepizole

4. A 49-year-old woman with no past medical history completed a marathon in 5 hours and 30 minutes. Along the run, she drank water frequently and ate energy bars at the various feeding stations. Four hours after completion of the marathon, she felt dizzy and nauseated, vomited three times, and was disoriented and confused. She was then admitted to the emergency department 7 hours after the symptoms occurred. Upon admission, the patient was conscious but disoriented. Her BP was 120/80 mmHg. The neurologic examination was not localizing. Her body weight was 55 kg. Four hours later, the patient had a generalized tonic-clonic seizure. A computed tomography (CT) scan showed a diffuse cerebral edema. Her laboratory results on admission to the emergency department were as follows: sodium, 122 mEq/L; potassium, 3.3 mEq/L; chloride, 88 mEq/L; bicarbonate, 22 mEq/L; creatinine, 0.9 mg/dl; BUN, 10 mg/dl; and glucose, 150 mg/dl. Urinalysis reveals osmolality of 320 mmol/kg, sodium of 110 mEq/L, and potassium of 40 mEq/L.

**The MOST likely cause of this patient’s polyuria is which ONE of the following?**

A. Glycosuria  
B. Urea osmotic diuresis  
C. Saline infusions  
D. Nephrogenic diabetes insipidus  
E. Surreptitious water ingestion

6. A patient has the following laboratory results: sodium, 140 mEq/L; potassium, 4.2 mEq/L; chloride, 80 mEq/L; bicarbonate, 24 mEq/L; BUN, 10 mg/dl; creatinine, 0.9 mg/dl; and glucose, 110 mg/dl. ABG reveals the following: pH 7.40; PO2, 100 mmHg; PCO2, 40 mmHg; and HCO3, 24 mEq/L.

**Which ONE of the following statements is correct?**

A. He has normal acid-base parameters.  
B. He has metabolic alkalosis and metabolic acidosis.  
C. He has chronic respiratory alkalosis.  
D. He has compensated metabolic alkalosis.

7. A 28-year-old Asian man enters the emergency department complaining of diffuse muscle weakness. He had eaten at a restaurant 2 hours before the sudden onset of his symptoms. He takes no medications and has no other history. His physical examination reveals a BP of 110/60 mmHg, heart rate of 90 beats per minute, and respiration rate of 15 per minute. He is afebrile. A musculoskeletal examination shows diffuse weakness. A neurologic examination shows diffusely
reduced reflexes, but no abnormal reflexes. Oriental x 3. His laboratory results reveal the following: sodium, 142 mEq/L; potassium, 1.8 mEq/L; chloride, 100 mEq/L; bicarbonate, 29 mEq/L; BUN, 12 mg/dl; creatinine, 0.8 mg/dl; and glucose, 120 mg/dl.

After treating his hypokalemia, you order which ONE of the following tests?
A. Plasma aldosterone  
B. Plasma renin  
C. Screen for cocaine  
D. Thyroid-stimulating hormone assay  
E. Serum cortisol

8. An 80-year-old woman who was treated long term with hydrochlorothiazide for hypertension was admitted with serum sodium of 110 mEq/L and serum potassium of 2.9 mEq/L. Her physical examination showed a BP of 110/65 mmHg supine and 90/60 mmHg standing, and a heart rate of 62 beats per minute. The patient was afebrile. The rest of the examination was unremarkable. There was no edema. Her laboratory results were as follows: sodium, 110 mEq/L; potassium, 2.9 mEq/L; chloride, 75 mEq/L; bicarbonate, 26 mEq/L; BUN, 24 mg/dl; and creatinine, 0.8 mg/dl. She was given isotonic saline and potassium replacement and a diuresis developed with a recorded urine output of 2400 ml in 6 hours. Her urine osmolality on admission was 410 mOsm/L but fell to 110 mOsm/L when urine output rose.

Which ONE of the following statements BEST explains the change in urinary findings?
A. Reduction in ADH responsiveness in the collecting duct  
B. Suppression of ADH secretion  
C. Suppression of ADH secretion and increased fluid delivery to the collecting duct  
D. Increased fluid delivery to the collecting duct  
E. Inhibition of sodium reabsorption in the thick ascending limb of Henle

9. Which ONE of the following mechanisms BEST explains the cause of nephrocalcinosis in patients with distal renal tubular acidosis?
A. Increased proximal tubular citrate reabsorption  
B. Hyperoxaluria  
C. Hypokalemia  
D. Reduced urine volume

10. A 45-year-old man developed hypernatremia after several days in the surgical intensive care unit, during which he received enteral care nutrition without sufficient free water. At this point you are asked to provide a prescription for correcting his free water deficit assuming no ongoing losses. His weight is 70 kg. His serum sodium is 155 mEq/L. He has no edema.

Restoring his serum sodium to 140 mEq/L will require which ONE of the following prescriptions?
A. 6.5 L of free water  
B. 2.5 L of free water  
C. 4.5 L of free water  
D. 8.5 L of free water

11. An 85-year-old woman who was treated with hydrochlorothiazide for hypertension was admitted with serum sodium of 106 mEq/L and serum potassium of 2.6 mEq/L. The thiazide was stopped, and she was given isotonic saline and potassium replacement; however, her serum sodium increased only by 2 mEq/L after 14 hours and her urine output was 60 ml/h. Therefore, 3% saline was prescribed. A few hours later, diuresis developed with a recorded urine output of 1950 ml in 7 hours and urine osmolality of 90 mOsm/kg. Her serum sodium was now 118 mEq/L, resulting in a rise of serum sodium of 12 mEq/L over 10 hours. At this point, all infusions were discontinued.

Which ONE of the following should now be ordered?
A. 5% dextrose in water at a rate to match urine output  
B. No further infusions  
C. Isotonic saline at a rate to match urine output  
D. 40 mg of furosemide intravenously
12. A 38-year-old man presents with a recent history of hypertension. He was seen by his primary care physician for a BP of 185/100 mmHg and began treatment with a thiazide diuretic but hypokalemia ensued. Thiazide use ended a month ago. He is referred to you for further evaluation. He is currently being treated with a calcium channel blocker. A physical examination shows a BP of 165/90 mmHg supine and standing, and a heart rate of 62 beats per minute. He is afebrile. The rest of the examination is unremarkable. There are no bruits and there is no edema. His laboratory studies show the following: sodium, 144 mEq/L; potassium, 3.1 mEq/L; chloride, 100 mEq/L; bicarbonate, 27 mEq/L; BUN, 16 mg/dl; and creatinine, 0.9 mg/dl.

At this point, which ONE of the following should be done?

A. Plasma aldosterone to renin ratio
B. Abdominal CT scan
C. 24-hour urinary aldosterone level
D. No further testing at this time

13. Assuming that an individual is maintained on a constant sodium, potassium, and fluid intake, which ONE of the following would BEST predict changes in serum sodium concentration in the ensuing 24 hours?

A. The ratio of urinary sodium to 24-hour urinary volume
B. The ratio of urinary sodium and urinary potassium to 24-hour urinary volume
C. The ratio of urinary osmolality to 24-hour urinary volume
D. The 24-hour urinary urea, sodium, and potassium to 24-hour urinary volume

14. A 68-year-old man is referred to you for evaluation of hypokalemia. He has a long history of esophageal reflux for which he has received esomeprazole for the past year. He has had no other medical problems and is additionally only taking 20 mg/d of atorvastatin. His physical examination shows a BP of 110/80 mmHg, heart rate of 80 beats per minute, and respiration rate of 15 breaths per minute. He is also afebrile. The patient’s examination is normal, save for some mild muscle weakness and decreased deep tendon reflexes. An electrocardiogram shows prominent U waves in the precordial leads. His laboratory results are as follows: sodium, 142 mEq/L; potassium, 2.2 mEq/L; chloride, 99 mEq/L; bicarbonate, 28 mEq/L; BUN, 12 mg/dl; creatinine, 0.8 mg/dl; and glucose, 110 mg/dl. Urinalysis is negative for blood, glucose, and protein. pH is 5.5. No formed elements are seen.

Which ONE of the following should now be done?

A. Plasma aldosterone to renin ratio
B. Serum magnesium
C. Transtubular potassium ratio
D. Platelet count
E. White blood cell count

15. Which ONE of the following statements regarding the use of oral sodium polystyrene sulfonate (SPS) for the treatment of hyperkalemia is correct?

A. SPS is no more effective than a placebo at reducing serum potassium in 24 hours in hyperkalemic patients.
B. SPS when given with sorbitol lowers serum potassium by a mean value of 0.6 mEq/L over the first 24 hours of use.
C. SPS when given with 70% sorbitol is a safe and effective therapy for acute hyperkalemia.
D. SPS raises stool potassium levels in the first 24 hours of therapy.

16. A 51-year-old woman is found to be hypertensive, with a BP of 200/105 mmHg. She was treated with diuretics and calcium channel blockers but her BP was poorly controlled. Her laboratory values show the following: sodium, 142 mEq/L; potassium, 2.8 mEq/L; chloride, 100 mEq/L; bicarbonate, 29 mEq/L; BUN, 16 mg/dl; and creatinine, 0.9 mg/dl. The plasma aldosterone to renin ratio was 35, with a plasma renin level of 0.6 ng/ml per hour.

At this point, which ONE of the following should be done?

A. Refer for surgery
17. A 14-year-old boy presents with hypokalemia. He experienced enuresis as a child and has grown poorly. He is at the 10th percentile for height. He denies taking any medications. His physical examination shows a BP of 105/80 mmHg, heart rate of 80 beats per minute, and respiration rate of 15 breaths per minute. He is afebrile. His laboratory results reveal the following: sodium, 140 mEq/L; potassium, 3.1 mEq/L; chloride, 99 mEq/L; bicarbonate, 31 mEq/L; BUN, 18 mg/dl; creatinine, 1.2 mg/dl; and glucose, 110 mg/dl. His urinalysis is negative for blood, glucose, and protein. pH is 5.5. No formed elements are seen. The urinalysis reveals the following: sodium, 90 mEq/L; potassium, 28 mEq/L; Ca, 290 mg/24 h; and chloride, 122 mEq/L.

Which ONE of the following statements regarding this patient is correct?
A. The patient has Bartter’s syndrome.
B. The patient has surreptitious vomiting.
C. The patient has Gitelman’s syndrome.
D. The patient has laxative abuse syndrome.

18. A 14-year-old boy is referred to you for treatment of his hypertension. He has been noted to be hypertensive for several years and has poorly adhered to therapy. He has a negative family history for hypertension. His physical examination shows a BP of 155/95 mmHg, heart rate of 84 beats per minute, and respiration rate of 17 breaths per minute. The rest of the examination is unremarkable. No bruits are heard. BP is similar in all extremities. His laboratory results are as follows: sodium, 140 mEq/L; potassium, 3.1 mEq/L; chloride, 98 mEq/L; bicarbonate, 30 mEq/L; BUN, 18 mg/dl; creatinine, 1.2 mg/dl; and glucose, 110 mg/dl. Urinalysis is negative for blood, glucose, and protein. pH is 5.5. No formed elements are seen. Urinalysis reveals the following: sodium, 90 mEq/L; and potassium, 28 mEq/L. Plasma renin is 0.1 ng/ml per hour, plasma aldosterone to plasma renin ratio is 50.

The patient’s MOST likely diagnosis is which ONE of the following?
A. Gordon’s syndrome
B. Liddle’s syndrome
C. Renal artery stenosis
D. Coarctation of the aorta
E. Low renin hypertension

19. A 47-year-old woman entered the hospital for treatment of chronic lymphocytic leukemia. She had noted increased weakness and easy bruising for the past 2 weeks. She was admitted for induction chemotherapy. Her physical examination showed a BP of 121/70 mmHg, heart rate of 88 beats per minute, and respiration rate of 15 breaths per minute. Her temperature was 98.7°F. Multiple ecchymoses of the skin and pallor of the mucous membranes were noted. An abdominal examination showed dullness and fullness in the left upper quadrant. Her laboratory results showed the following: sodium, 142 mEq/L; potassium, 6.4 mEq/L; chloride, 99 mEq/L; bicarbonate, 20 mEq/L; BUN, 15 mg/dl; creatinine, 0.8 mg/dl; glucose, 95 mg/dl; hemoglobin, 6.1 g/dl; white blood cells, 98,000 cells/μL 100% blasts; and platelets, 14,000/μL.

At this point, which ONE of the following would you recommend?
A. Measure plasma potassium
B. Administer calcium chloride
C. Administer sodium bicarbonate
D. Administer kayexalate
E. Administer furosemide

20. A 19-year-old woman with a history of alcoholism presented to her local emergency department 22 hours after ingesting as large quantity of 500-mg acetaminophen tablets (total dose of 112.5 g). The patient’s plasma acetaminophen level at the local emergency department was elevated at 210 μg/L (reference range <50 μg/L). N-acetylcysteine (NAC) infusion therapy was initiated as was ventilatory support. On physical
examination, she was lethargic. Her BP was 145/87 mmHg, heart rate was 124 beats per minute, and respiratory rate was 23 breaths per minute. The rest of her physical examination was unremarkable. The patient completed her course of NAC (per protocol) and an accompanying bicarbonate infusion. Her laboratory results were as follows: sodium, 128 mEq/L; potassium, 3.1 mEq/L; chloride, 92 mEq/L; bicarbonate, 6 mEq/L; BUN, 5 mg/dl; creatinine, 0.4 mg/dl; and glucose, 110 mg/dl. ABG showed the following: pH 7.0, PO$_2$, 133 mmHg; PCO$_2$, 18 mmHg; and HCO$_3$, 4 mmol/L. Her aspartate aminotransferase was 475 U/L (normal range, 8–43 U/L) and alanine aminotransferase was 358 U/L (normal range, 7–45 U/L). The patient’s lactate level was 3 mmol/L and her β-hydroxybutyrate was 1 mmol/L. Her results were negative for ethanol, methanol, and ethylene glycol.

One day after admission, the serum anion gap normalized. By the time of discharge (8 days after admission), the serum bicarbonate normalized. The MOST likely cause of her metabolic acidosis was which ONE of the following?

A. D-lactic acidosis
B. Paraldehyde acidosis
C. Toluene ingestion
D. Pyroglutamic acidosis

21. A 68-year-old man presents with a recent history of falling several times at home. He was admitted to the hospital for evaluation when a serum sodium of 114 mEq/L was noted in the emergency department. He is confused about current events. He weighs 70 kg. His physical examination shows a BP of 110/77 mmHg and heart rate of 75 beats per minute. The patient is afebrile. The rest of the examination is unremarkable. There is no edema. His laboratory studies show the following: sodium, 114 mEq/L; potassium, 4.2 mEq/L; chloride, 83 mEq/L; bicarbonate, 25 mEq/L; BUN, 6 mg/dl; and creatinine, 0.6 mg/dl. He is placed on a strict fluid limit of 1 L/d.

Assuming a fixed solute intake, which ONE of the following 24-hour urinary values will result in a rise of serum sodium of at least 5 mEq/L in the next 48 hours?

A. Urinary sodium, 80 mEq/L; urinary potassium, 40 mEq/L; urinary volume, 2 L
B. Urinary sodium, 40 mEq/L; urinary potassium, 5 mEq/L; urinary volume, 2 L
C. Urinary sodium, 40 mEq/L; urinary potassium, 60 mEq/L; urinary volume, 2 L
D. Urinary sodium, 60 mEq/L; urinary potassium, 60 mEq/L; urinary volume, 2 L

22. A 38-year-old woman entered the emergency department with weakness, frequent urination, intermittent vomiting, dysphagia, and increased thirst and fluid intake. Her only past history was a diagnosis of breast cancer, for which she had surgery and radiation therapy 5 years earlier. On physical examination, she had a temperature of 37.2°C, heart rate of 89 beats per minute, BP of 100/60 mmHg supine and 88/50 mmHg upright, and respiratory rate of 18 breaths per minute. Her mucous membranes were dry. The rest of the examination was noncontributory. She was admitted to the hospital. Her laboratory studies revealed the following: sodium, 156 mEq/L; potassium, 3.7 mEq/L; chloride, 123.0 mEq/L; bicarbonate, 24.0 mEq/L; creatinine, 0.9 mg/dl; BUN, 22.0 mg/dl; glucose, 130 mg/dl; and calcium, 9.1 mg/dl. Urine osmolality was 88.0 mmol/kg.

Which ONE of the following would MOST likely reveal the cause of her electrolyte disorder?

A. Fluid deprivation test
B. Plasma cortisol assay
C. Serum thyroid-stimulating hormone assay
D. Magnetic resonance imaging of the brain

23. A 61-year-old woman entered the emergency department with a complaint of a feeling of impending doom. Five days ago, she saw her family doctor and was given a prescription for trimethoprim/sulfa for an upper respiratory tract infection. He measured a metabolic profile at that time and told her that her laboratory results, including electrolytes and glucose, were all within the normal range. Before her entry into the emergency department, she experienced an acute increase
in the generalized weakness, rendering her unable to stand without assistance. The patient’s past medical history was significant for diabetes and stage 4 CKD (estimated GFR of 25 ml/min per 1.73 m²). Her current medications were glyburide and lisinopril. On physical examination, she had a BP of 190/65 mmHg, heart rate of 100 beats per minute, and respiration rate of >20 breaths per minute. Cardiac examination was unremarkable for any pertinent findings other than tachycardia. Her neurologic examination showed significant generalized weakness throughout and 2/5 strength in all extremities. She was mentating normally. Her laboratory results revealed the following: sodium, 142 mEq/L; potassium, 7.8 mEq/L; chloride, 100 mEq/L; bicarbonate, 19 mEq/L; BUN, 52 mg/dl; and creatinine, 3.9 mg/dl.

The MOST likely primary cause of her hyperkalemia is which ONE of the following?

A. Interference with normal transport through the epithelial sodium channel in the collecting duct
B. Interference with normal transport by the basolateral sodium-potassium ATPase in the collecting duct
C. Decreased sodium chloride delivery to the collecting duct
D. Reduce aldosterone levels
E. Blockade of the epithelial growth factor receptor

24. A 24-year-old man with hypertension is referred to you for evaluation of his hypokalemia. He has been hypertensive since at least age 13 years and had a stroke at age 17 years. He is fully recovered. He has been treated with a variety of agents but is often found to be quite hypertensive when he monitors his home BP readings. He has a strong family history of hypertension on his father’s side (with his father, uncle, and aunt all having severe hypertension) and his father had a stroke at age 34 years. His physical examination shows a BP of 185/98 mmHg supine and standing, and a heart rate of 62 beats per minute. He is afebrile. The rest of the examination is unremarkable. There are no bruits, and there is no edema. His laboratory results are as follows: sodium, 140 mEq/L; potassium, 3.1 mEq/L; chloride, 98 mEq/L; bicarbonate, 30 mEq/L; BUN, 18 mg/dl; creatinine, 1.2 mg/dl; and glucose, 110 mg/dl. Urinalysis is negative for blood, glucose, and protein. pH is 5.5. No formed elements are seen. Plasma renin is 0.1 ng/ml per hour, plasma aldosterone is 19 ng/ml, and the plasma aldosterone to plasma renin ratio is 190.

At this time, which ONE of the following should you order?

A. Treatment with dexamethasone
B. Treatment with spironolactone
C. Treatment with renal nerve ablation
D. CT scan of the abdomen
E. CT angiogram of the renal vasculature

25. A 39-year-old Asian man presented to the emergency department with paralysis of all extremities on awakening in the morning. He had noticed mild muscle weakness of his lower extremities for 2 days. He denied vomiting, diarrhea, and the use of diuretics. He also did not have hyperthyroidism or a previous episode of paralysis. He noticed a problem with a burning sensation of his eyes. He had a BP of 110/70 mmHg, heart rate of 68 beats per minute, and respiratory rate of 18 breaths per minute. He was afebrile. The thyroid gland was not enlarged. Neurologic examination revealed symmetrical flaccid paralysis and areflexia of all four limbs without fasciculation, myoclonus, or muscular atrophy. The remainder of the physical examination was unremarkable. His laboratory results were as follows: sodium, 138 mEq/L; potassium, 1.6 mEq/L; chloride, 117 mEq/L; bicarbonate, 8 mEq/L; BUN, 15 mg/dl; creatinine, 2.0 mg/dl; and glucose, 95 mg/dl. Urinalysis showed pH 6, protein (2+), blood (2+), sodium of 45 mEq/L, potassium of 20 mEq/L, and chloride of 70 mEq/L.

The MOST likely cause of his acid-base disturbance is which ONE of the following?

A. Surreptitious laxative abuse
B. Sjögren’s syndrome
C. Bartter’s syndrome
D. Gitelman’s syndrome
E. Diuretic abuse

26. A 31-year-old man developed metastatic testicular cancer for which he received several courses of chemotherapy including etoposide, ifosfamide, and carboplatinum over the past 3 months. He now presents with complaints of weakness and nocturia. A recent positron emission tomography/CT examination revealed no evidence of malignant tissue metabolic activity. Physical examination shows a thin man in no acute distress. His BP is 108/60, respiration rate is 15 breaths per minute, and heart is 86 beats per minute. He is afebrile. He shows mild diffuse muscle weakness. His laboratory results are as follows: sodium, 134 mEq/L; potassium, 2.9 mEq/L; chloride, 105 mEq/L; bicarbonate, 14 mEq/L; BUN, 18 mg/dl; creatinine, 1.4 mg/dl; and glucose, 110 mg/dl. His urinalysis reveals pH 5.0, protein (1+), and glucose (1+) and is negative for blood. In addition, his urine sodium is 90 mEq/L, urine potassium is 28 mEq/L, and urine chloride is 110 mEq/L.

The MOST likely cause of his electrolyte abnormalities is which ONE of the following?
A. Surreptitious laxative abuse
B. Proximal renal tubular acidosis (RTA)
C. Distal RTA
D. Type IV RTA

27. A 22-year-old woman with a history of alcoholism presented to the emergency department in extremis. She had been on an alcoholic binge and was brought in by a friend after she was found on the floor of her apartment. On physical examination, she was lethargic. She had a BP of 150/90 mmHg, heart rate of 100 beats per minute, and respiratory rate of 26 breaths per minute. The rest of her physical examination was unremarkable. Her laboratory results were as follows: sodium, 132 mEq/L; potassium, 3.7 mEq/L; chloride, 92 mEq/L; bicarbonate, 8 mEq/L; BUN, 10 mg/dl; creatinine, 0.4 mg/dl; and glucose, 110 mg/dl. ABG revealed the following: pH 7.20; PO\textsubscript{2}, 100 mmHg; PCO\textsubscript{2}, 21 mmHg; and HCO\textsubscript{3}, 9 mEq/L. Microscopic exam of the urine (see Figure 1).

The MOST likely cause of this patient’s metabolic disorder is which ONE of the following?
A. Ethylene glycol intoxication
B. Methanol
C. Isopropyl alcohol intoxication
D. Toluene sniffing

28. A 65-year-old man presents with a recent history of some confusion and unsteady gait. He was admitted to the hospital for evaluation of a serum sodium level of 108 mEq/L. He is mentating slowly and is confused about current events. A physical examination shows a BP of 115/70 mmHg and a heart rate of 72 beats per minute. He is afebrile. The rest of the examination is unremarkable. There is no edema. His laboratory studies show the following: sodium, 114 mEq/L; potassium, 3.9 mEq/L; chloride, 80 mEq/L; bicarbonate, 26 mEq/L; BUN, 10 mg/dl; and creatinine, 0.8 mg/dl. Urinalysis reveals the following: sodium, 110 mEq/L; potassium, 20 mEq/L; volume, 1 L/d; and osmolality, 410 mOsm/L. You decide to treat the patient with 3% sodium chloride to improve his mental status.

Which ONE of the following should be your goal?
A. Serum sodium no higher than 120 mEq/L by 12 hours after initiation of therapy
29. An 18-year-old man presents with the complaint of nocturia and polyuria. He states this has been a problem for as long as he can remember. His 24-hour urine volume is 4.2 L. He has no other medical history. He plays football on his high school team. There is no family history of renal disease. Both parents are alive and well, and he has two healthy siblings. A physical examination shows a BP of 115/70 mmHg and a heart of 72 beats per minute. He is afebrile. The rest of the examination is unremarkable. There is no edema. Laboratory studies show the following: sodium, 136 mEq/L; potassium, 3.9 mEq/L; chloride, 95 mEq/L; bicarbonate, 26 mEq/L; BUN, 10 mg/dl; and creatinine, 0.8 mg/dl. Urinalysis reveals the following: sodium, 11 mEq/L; potassium, 20 mEq/L; volume, 4.2 L/d; and osmolality, 110 mOsm/L.

At this point, which ONE of the following should you order?
A. Desmopressin infusion
B. Magnetic resonance imaging of brain
C. Water deprivation study
D. Low-salt diet
E. Renal ultrasonography

30. A 22-year-old female student noted proximal muscle weakness in the morning and had difficulty in getting up from a squatting position. The weakness progressed over a few hours and she experienced difficulty in turning in bed, swallowing, and speaking. She had suffered from fever and cough 5 days before this illness, which had lasted for 2 days. On physical examination, she was drowsy and was barely able to move or speak. She had a BP of 150/50 mmHg, an irregular heart rate of 96 beats per minute, and a respiratory rate of 40 breaths per minute. She had flaccid quadriplegia. Biceps, triceps, knee, and ankle reflexes were absent. Her laboratory results were as follows: sodium, 134 mEq/L; potassium, 1.6 mEq/L; chloride, 110 mEq/L; bicarbonate, 15 mEq/L; BUN, 18 mg/dl; creatinine, 0.9 mg/dl; and glucose, 110 mg/dl. Urinalysis was negative for blood, glucose, and protein. pH was 7.0. No formed elements were seen.

Which ONE of the following should this patient now receive as initial therapy?
A. Sodium bicarbonate infusion
B. Potassium chloride infusion
C. Mechanical ventilation
D. Oral potassium citrate

Core Knowledge Questions

Fluid, Electrolyte, and Acid-Base Disturbances

1. A 26-year-old man presents to the emergency department because of tetraparesis. He had ingested three packages of candy within a few hours before the onset of weakness. Physical examination reveals a pulse of 116 bpm and BP of 148/80 mmHg. His hands are sweating. He is noted to have fullness in the neck area. There is no family history of similar complaints, and the patient has not previously experienced these symptoms. Deep reflexes are absent without sensory changes. Laboratory studies reveal the following: Na, 140 mmol/L; K, 2.0 mmol/L; Cl, 100 mmol/L; HCO$_3$- 24 mEq/L; BUN, 10 mg/dl; and creatinine, 1.0 mg/dl. Urine electrolytes are as follows: Na, 102 mmol/L; K, 12 mmol/L; and Cl, 98 mmol/L. Free T4 is 56 pmol/L (n11.4) and thyroid-stimulating hormone is 0.01 (0.39 and 1.8 mIU/L).

Which ONE of the following statements is CORRECT with regard to this patient?
A. The development of hypokalemia and paralysis in such a patient occurs more commonly in women.
B. Potassium should be given in a solution containing 5% dextrose in water at a rate not to exceed 10 mmol/h.
C. His condition is unique to Graves’ disease.
D. The patient is at increased risk for recurrent attacks after the hyperthyroid state is corrected.
E. The serum Mg and PO$_4$ are likely to be low in this patient.

2. A 16-year-old girl is referred with a provisional diagnosis of primary aldosteronism. Her BP is consistently elevated at 180/120 mmHg, serum K is 2.6 mmol/L, and serum HCO$_3$- is 30 mmol/L. The patient’s younger brother has a BP of 200/110 mmHg, serum K of 2.7 mmol/L, and serum HCO$_3$- of 29 mmol/L. During the next several years, the patient develops renal failure as a result of poorly controlled BP. The patient receives a successful renal allograft from a nonrelated deceased donor. After the transplant, the patient is no longer hypertensive and electrolytes are normal.

Which ONE of the following is the MOST likely cause of the patient’s original disease?
A. Activating mutation in the WNK4 kinase
B. Inactivating mutation of WNK1 kinase
C. Inactivating mutation in the mineralocorticoid receptor
D. Truncating mutation causing deletion of the carboxy tail of the β subunit of the epithelial Na channel
E. Mutation in the Na$^+$.K$^+$.2Cl$^-$ cotransporter

3. A 19-year-old man is referred for management of his difficult-to-control hypertension. His brother has difficult-to-control hypertension, and his father had severe hypertension and died of a stroke at age 33 years. The patient seems healthy but has a BP of 180/110 mmHg. Grade 2 hypertensive retinopathy is present on funduscopic examination. Laboratory studies reveal the following: Na, 140 mmol/L; K, 2.2 mmol/L; Cl, 90 mmol/L; HCO$_3$-, 36 mEq/L; plasma renin activity, 0.2 ng/ml per hour (3–9 ng/ml per hour), and aldosterone, 18 ng/dl (nl <10). Plasma 18-OH cortisol is markedly elevated. High-resolution tomography of the abdomen is negative for adrenal masses.

Which ONE of the following is the MOST specific treatment of the patient’s condition?
A. Spironolactone
B. Dexamethasone
C. Amiloride  
D. Angiotensin converting enzyme inhibitor  
E. Calcium channel blocker

4. A 30-year-old man, despondent over a recently diagnosed brain tumor, goes on a drinking binge and consumes several quarts of beer in a short period. He is complaining of a headache and vomiting and is mildly confused. On physical examination, his weight is 100 kg, BP is 120/80 mmHg, and heart rate is 100 bpm. There is no jugular venous distention, pupils are equal and reactive, ocular fundi are normal, chest is clear, heart has no gallop, there is no edema, and there are no focal neurologic findings. His laboratory data are as follows: serum Na, 122 mmol/L; serum K, 3.2 mmol/L; serum Cl, 88 mmol/L; serum HCO₃, 29 mmol/L; BUN, 4 mg/dl; creatinine, 0.6 mg/dl; glucose, 90 mg/dl; osmolality, 270 mOsm/kg; aspartate aminotransferase, 220; alanine aminotransferase, 80; bilirubin, 2.2; alkaline phosphatase, 120; urine Na, 150 mmol/L; and urine osmolality, 420 mOsm/kg.

Which ONE of the following is the BEST initial therapy?  
A. 100 ml of 3% saline over 15 minutes, times three  
B. 3% saline at 20 ml/h for 24 hours  
C. Fluid restriction  
D. Isotonic saline 1 L over 1 hour  
E. Conivaptan 20-mg bolus

5. A 50-year-old man with hepatic cirrhosis develops progressive edema and ascites while taking 100 mg/d of spironolactone. His serum potassium is 4.5 mmol/L and his serum creatinine is 0.6 mg/dl. A spot urine sample shows a urine Na concentration of 40 mmol/L and a urine creatinine concentration of 100 mg/dl.

Which ONE of the following is the BEST approach?  
A. Continue the current dosage of spironolactone and request a dietary consultation to instruct the patient in a low-sodium diet.  
B. Increase the dosage of spironolactone to 200 mg/d.  
C. Order a large-volume paracentesis.  
D. Start 40 mg of furosemide twice daily and continue spironolactone.  
E. Start 40 mg of furosemide twice daily and discontinue spironolactone.
Answers and Explanations

1. **Answer E: The serum Mg and PO$_4$ are likely to be low in this patient.**

   The patient presents with signs and symptoms consistent with hypokalemic periodic paralysis (HPP). HPP can be an acquired disorder developing in association with hyperthyroidism. The acquired form of HPP is much more common in men, making choice A incorrect. Choice B is incorrect because potassium supplements in the acute attack should be given in nondextrose-containing solutions because insulin release can actually make the hypokalemia worse. Thus, choice B is incorrect. Choice C is incorrect because HPP can occur in association with hyperthyroidism due to any underlying cause such adenomas. Choice D is incorrect because the disease is cured once the hyperthyroid state is corrected. In the acquired form of the disease, low Mg and PO$_4$ are often present due to a shift into the cell similar to what occurs with K, making choice E the correct answer.


2. **Answer D: Truncating mutation causing deletion of the carboxy tail of the β subunit of the epithelial Na channel.**

   The hypokalemic metabolic alkalosis accompanied by hypertension and the positive family history are consistent with Liddle’s syndrome. This disorder is caused by mutations that present as if there is constitutive activation of the epithelial Na channel. Mutations in the carboxy tail of either the β or γ subunit of the channel are known to cause the syndrome. Renal transplantation in the index case of Liddle’s syndrome was curative of the electrolyte disorders. WNK4 or WNK1 mutation does not cause Liddle’s syndrome. Inactivating mutations in WNK4 or activating mutations in WNK1 have been described as a cause of Gordon’s syndrome, making choices A and B incorrect. Gordon’s syndrome presents with hyperkalemia, normal gap acidosis, and hypertension. Inactivating mutations in the mineralocorticoid receptor present with hyperkalemia, normal gap acidosis, and normal or low BP, making choice C incorrect. Choice E is incorrect because mutations in the Na-K-2Cl cotransporter give rise to Bartter’s syndrome. Hypertension is not a feature of Bartter’s syndrome.


3. **Answer B: Dexamethasone.**

   The patient presents with hypokalemic metabolic alkalosis and hypertension in the setting of having similarly affected family members. The work-up of the patient is positive for increased plasma aldosterone and suppressed plasma renin activity. An adrenal adenoma, bilateral adrenal hyperplasia, and dexamethasone suppressible hyperaldosteronism are considerations in this case. The positive family history and increased plasma 18-OH cortisol confirms the diagnosis of dexamethasone suppressible hyperaldosteronism, making choice B the correct answer. Choice A would be an effective therapy by blocking the effects of increased aldosterone but unlike dexamethasone, spironolactone is not the most specific therapy. For similar reasons, amiloride (choice C) is also not the correct answer. An angiotensin converting enzyme inhibitor or a calcium channel blocker (choices D and E) would help treat the hypertension but would not be specific therapies of the underlying disorder.

4. **Answer A: 100 ml 3% saline over 15 minutes, times three.**
The patient has symptomatic hyponatremia associated with intracranial pathology and is therefore at risk for herniation. The history suggests self-induced acute water intoxication with the potential for delayed absorption of ingested electrolyte-free water. The high urine sodium concentration (higher than plasma) indicates that fluid restriction (choice C) and isotonic saline (choice D) will be ineffective. Conivaptan (choice E) has been used to treat hyponatremia in neurointensive care units, but a third of patients respond with an increase in serum sodium concentration <4 mEq/L, and therefore the drug cannot be recommended for a crisis situation. The most reliable therapy is 3% NaCl. A slow infusion (choice B) is appropriate for chronic hyponatremia with mild symptoms. A bolus infusion (choice A) has been used successfully to treat impending herniation in normonatremic neurosurgery patients and has become a consensus recommendation for emergency therapy.


5. **Answer D: Start furosemide 40 mg twice daily and continue spironolactone**
The patient has an inadequate response to monotherapy with spironolactone for edema and ascites caused by hepatic cirrhosis. His urine sodium concentration of 40 mmol/L with a urine creatinine concentration of 100 mg/dl suggests that daily urine sodium losses are <40 mmol, barely matching intake from a 2-g sodium diet. Attempting to manage the problem with dietary interventions (choice A) is unlikely to work. Guidelines from the American Association for the Study of Liver Diseases advocate combinations of furosemide and spironolactone for the management of ascites. Recent studies have shown that beginning with combined treatment is preferable because it achieves more rapid resolution of ascites with a lower incidence of hyperkalemia than a strategy of beginning with spironolactone alone and adding furosemide if diuretic resistance were encountered. Therefore, increasing the dose of spironolactone (choice B) will be less effective and risks hyperkalemia. Large-volume paracentesis (choice C) should be reserved for patients who are diuretic resistant. Furosemide alone (choice E) is ill advised because it risks hypokalemia which can cause hepatic encephalopathy.