The difficulty that nonnephrologists sometimes have with the differential diagnosis of hyponatremic patients often results from misinterpreting the significance of measured and calculated serum osmolalities, effective serum osmolalities (tonicities), and the influence of various normal (eg, serum urea nitrogen) and abnormal (eg, ethanol) solutes. Among the more commonly held misconceptions are that high serum urea or alcohol levels will, by analogy with glucose, cause hyponatremia, and that a normal (or elevated) measured serum osmolality in a hyponatremic patient excludes the possibility of hypotonicity. This article describes typical and deliberately comparative data of the serum levels of sodium, glucose, urea nitrogen, and mannitol and/or ethanol (if present); calculated and measured osmolality; effective osmolality; and the potential risk of hypotonicity-induced cerebral edema for each of 6 prototypical hyponatremic states. This provides a helpful educational tool for untangling these interrelationships and for clarifying the differences among various hyponatremic conditions.

Nonnephrologists, as well as house staff and other trainees, frequently have difficulty with the differential diagnosis in hyponatremic patients and with assessing their relative risk for developing cerebral edema. This difficulty often derives from misinterpreting (1) the measured and calculated serum osmolalities, (2) the effective serum osmolalities (tonicities), and (3) the influences of other normal and abnormal solutes. The confusion relates not only to the concepts but to the details of calculation and assessment. Some of the most commonly held misconceptions are shown in Table 1.

This article will clarify the interrelationships of serum sodium, serum glucose, serum urea nitrogen (SUN), and serum mannitol and/or ethanol (if present) concentrations; calculated and measured serum osmolality; effective serum osmolality; and potential risk of cerebral edema (induced by hypotonicity) in various clinic settings. The focal point for the discussion is Table 2, which provides typical and deliberately comparative laboratory data for each condition.

DEFINITION OF TERMS

True hyponatremia is a reduction in serum sodium concentration to below the lower limit of normal, which results from a decrease in sodium content per unit volume of water. In true hyponatremia (Table 3), total body sodium and total body water levels may be decreased, normal, or increased, whereas in pseudohyponatremia these variables are unchanged from normal.

Pseudohyponatremia is a method-dependent, artifactual reduction of serum sodium concentration resulting from displacement of a portion of the water phase of the plasma by lipid (eg, in severe hypertriglyceridemia) or by protein (eg, in multiple myeloma). This problem (which may be observed with flame emission spectrometry) can be avoided by using a sodium-selective electrode without dilution.

Calculated serum osmolality (Osm,) is the osmolality estimated by using various equations that include the sum of the contributions of sodium, urea, and glucose. (For the purposes of this discussion, we neglect the differences between osmolality and osmolarity. The small error caused by failing to use the correction factor for serum water content in these conversions is clinically unimportant.) We have used the
Table 1. Common Fables

1. That the presence of true hyponatremia means that the total body water must always be increased, that the total body sodium must always be decreased, or both.
2. That high serum urea or alcohol levels will, by analogy with glucose, cause hyponatremia.
3. That urea and alcohol do not contribute to measured serum osmolality.
4. That a normal (or elevated) measured serum osmolality in a hyponatremic patient excludes the possibility of hypotonicity.
5. That a patient with hyperglycemia-induced hyponatremia must have a normal measured serum osmolality.
6. That the presence or absence of an abnormally increased osmolal gap provides definitive information regarding whether a hyponatremic patient is at increased risk for cerebral edema.

*Some of these misconceptions are held concurrently despite mutual incompatibility. These fables have been debunked as follows: No. 1, see discussion of true hyponatremia and Table 3; No. 2 to 4, see discussion of cases 6 and 7 in Table 2; No. 5, see discussion of case 4 in Table 2; and No. 6, compare cases 5 and 7 in Table 2 and compare cases 1, 2, and 4 in Table 2.

The osmolal gap is the difference between the measured and the calculated osmolality (Osmm − Osmc).7,8

According to Dorwart and Chalmers,7 the average (± SD) osmolal gap in normal individuals with the use of molar units has a negative value (−9.0 ± 6.4 mmol/L). Although a range of normal values has not been defined, positive values in excess of 10 mmol/kg H2O are considered to be clearly abnormal. To simplify the comparisons in Table 2, we assume that the average normal osmolal gap in each case is 0 mmol/kg H2O (a value within the normal range), and that values greater than 10 mmol/kg H2O are abnormally high.

Effective osmolality, a term synonymous with tonicity, is that portion of total osmolality that has the potential to induce transmembrane water movement.9,12,14 Substances (such as urea and ethanol) that easily cross cell membranes and contribute to measured osmolality, but not to tonicity, are called ineffective solutes.9,11,12,14 In contrast, effective solutes (such as sodium and mannitol) are confined largely to the extracellular fluid (ECF) compartment and contribute to both measured osmolality and tonicity. Effective osmolality can be estimated from clinical data, but its value is not actually measured in clinical laboratories. For ease of comparison, we have calculated the values of effective osmolality cited in the table by subtracting the contributions of urea (and ethanol, if present) from the measured osmolality.

The risk of cerebral edema refers to the immediate likelihood that, before treatment, water will move from the ECF into the intracellular fluid compartment of the brain, thereby producing the osmotic type of cerebral edema. When the effective osmolality of the ECF is low in comparison to that of the intracellular fluid, there is an increased risk of cerebral edema. In Table 2, the relative risk in various abnormalities is compared with the absence of risk in a normal individual. When the effective osmolality of the ECF is low in comparison with that of the intracellular fluid, there is an increased risk of cerebral edema.

DESCRIPTION OF PROTYPIC CONDITIONS

Table 2 is constructed to illustrate typical values for normal individuals and for patients with each of 7 pathological conditions, 6 of which are associated with hyponatremia. Data are provided for serum sodium, serum glucose, SUN, serum mannitol or ethanol (if either is present), Osmc, Osmm, osmolal gap, and effective osmolality, as well as the risk of cerebral edema. For illustrative consistency, the normal (typical) values of the variables are chosen as follows: serum sodium, 140 mmol/L; serum glucose, 5 mmol/L (90 mg/dL); SUN, 3 mmol/L (14 mg/dL); Osmc, 290 mmol/kg H2O; Osmm, 290 mmol/kg H2O; osmolal gap, 0 mmol/kg H2O; and effective osmolality, 285 mmol/kg H2O. All of the hyponatremic states are arbitrarily given a serum sodium level of 120 mmol/L.

Normal

The Osmc is \((2)(140) + 5 + 5 = 290\) mmol/kg H2O. Because, as mentioned above, the normal osmolal gap is arbitrarily set at 0 mmol/kg H2O, the Osmm is also 290 mmol/kg H2O. The effective osmolality is 290 mmol/kg H2O minus the 5-mmol/kg H2O contribution of urea, ie, 285 mmol/kg H2O. Because the effective osmolality (or tonicity) is normal, there is no risk of cerebral edema.

True Hyponatremia

The Osmc is \((2)(120) + 5 + 5 = 250\) mmol/kg H2O, a value that is lower than normal; the Osmm is also 250 mmol/kg H2O, so the osmolal gap is 0 mmol/kg H2O. In this case, the effective osmolality is 250 – 5, ie, 245 mmol/kg H2O, an abnormally low value that indicates increased susceptibility to cerebral edema. Patients who are hypo-osmolar must also be hypotonic, but even patients who are either normo-osmolar or hyperosmolar may still be hypotonic (see the examples given below of true hyponatremia together with either a high SUN level or a high serum ethanol level).

Pseudohyponatremia

In a patient with profound hypertriglyceridemia, as discussed above, the serum sodium concentration (depending on the method of analysis; see “Definitions of Terms” section, above) might be reduced to 120
Table 2. Typical Serum Sodium, Osmolality, and Effective Osmolality (Tonicity) in Different Clinical States

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Condition</th>
<th>Serum Sodium, mmol/L</th>
<th>Blood Glucose, mmol/L</th>
<th>Serum Urea Nitrogen, mmol/L</th>
<th>Mannitol or Ethanol, mmol/L</th>
<th>Osmc, mmol/kg H2O</th>
<th>Osmm, mmol/kg H2O</th>
<th>Osmal Gap, mmol/kg H2O</th>
<th>Effective Osmolality, mmol/kg H2O</th>
<th>Risk of Cerebral Edema‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>140</td>
<td>5 (90) 5 (14)</td>
<td>0</td>
<td>290</td>
<td>290</td>
<td>250</td>
<td>40</td>
<td>285 (Normal)</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Hyponatremia (without abnormal amounts of other solutes)</td>
<td>120</td>
<td>5 (90) 5 (14)</td>
<td>0</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>40</td>
<td>245 (Low)</td>
<td>Increased</td>
</tr>
<tr>
<td>3</td>
<td>Pseudohyponatremia (eg, from extreme hyperglycemia)</td>
<td>120</td>
<td>5 (90) 5 (14)</td>
<td>0</td>
<td>250</td>
<td>290</td>
<td>40</td>
<td>245 (Low)</td>
<td>285 (Normal)</td>
<td>Unchanged</td>
</tr>
<tr>
<td>4</td>
<td>Hyponatremia caused by severe hyperglycemia</td>
<td>120</td>
<td>75 (1350) 5 (14)</td>
<td>0</td>
<td>320</td>
<td>320</td>
<td>0</td>
<td>315 (High)</td>
<td>Variable§</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Hyponatremia caused by retention of mannitol</td>
<td>120</td>
<td>5 (90) 5 (14)</td>
<td>75</td>
<td></td>
<td></td>
<td>250</td>
<td>325</td>
<td>75</td>
<td>320 (High)</td>
</tr>
<tr>
<td>6</td>
<td>Hyponatremia together with high serum urea nitrogen¶</td>
<td>120</td>
<td>5 (90) 45 (126)</td>
<td>0</td>
<td>290</td>
<td>290</td>
<td>0</td>
<td>245 (Low)</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Hyponatremia together with high blood ethanol level¶</td>
<td>120</td>
<td>5 (90) 5 (14)</td>
<td>40#</td>
<td>250</td>
<td>290</td>
<td>40</td>
<td>245 (Low)</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Hyponatremia†</td>
<td>160</td>
<td>5 (90) 5 (14)</td>
<td>0</td>
<td>330</td>
<td>330</td>
<td>0</td>
<td>325 (High)</td>
<td>Decreased</td>
<td></td>
</tr>
</tbody>
</table>

* Osmc indicates calculated osmolality (calculated as 2[Na] + SUN/2.8 + GLU/18, where SUN indicates serum urea nitrogen, and GLU, glucose). Osmm, measured osmolality (we assume herein that the normal osmolar gap is zero). Osmal gap is Osmm – Osmc.

†Effective osmolality (tonicity) is that portion of osmolality inducing transmembrane water movement; the cited values for effective osmolality were calculated by subtracting the contributions of urea and ethanol (if present) from the measured osmolality.

‡Immediate risk of the osmotic type of cerebral edema before treatment. (The more acute the hyponatremia, the greater the risk, since osmotic adaptation is less advanced.)

§Effect on intracellular fluid volume depends on clinical circumstances.

¶Neglecting the correction factor for serum water content, 75 mmol of mannitol per liter corresponds to approximately 1365 mg/dL.

‡Immediate risk of cerebral dehydration. Other outcomes are possible, however, depending on clinical circumstances.

Therefore, the absence of an increased osmolar gap rules out pseudo-hyponatremia.

Hyponatremia Caused by Severe Hyperglycemia

The hyponatremic response to hyperglycemia is variable and determined by several factors, most of which are not known or measurable during the usual clinical circumstances. Therefore, we used the correction factor of Katz, whereby the serum sodium level decreases by 1.6 mmol/L for each 5.6 mmol/L (100 mg/dL) increase in glucose level. Use of this formulation in Table 2 predicts that elevation of the serum glucose level has induced a translocation of water from the intracellular fluid to the ECF sufficient to reduce the serum sodium level to approximately 120 mmol/L (a reduction from 140 mmol/L as does glucose, a serum mannitol concentration of 75 mmol/L (1365 mg/dL) might be expected to be associated with a serum sodium level of approximately 120 mmol/L. As in the case of hyperglycemia, we are neglecting the effect of any osmotic diuresis on the serum sodium concentration. The Osmm, which does not take mannitol into account, will be (2)(120) + 75 + 5 = 320 mmol/kg H2O, an abnormally low value. (Note that this contrasts with

Table 3. True Hyponatremia*

<table>
<thead>
<tr>
<th>Total Body Sodium</th>
<th>Total Body Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* These combinations of total body sodium and total body water all produce true hyponatremia; of course, any combination of total body sodium depletion together with total body water excess will also produce true hyponatremia. A downward arrow indicates decreased; an upward arrow, increased.

†Use of 2 arrows indicates a greater degree of abnormality.

‡O indicates normal (unchanged).

mmol/L. If the SUN and serum glucose levels are normal, this must result in a subnormal Osmc; in this example, the Osmc will be (2)(120) 5 5 + 5 = 250 mmol/kg H2O. An osmometer measures solutes only in the water phase of serum, and therefore the measurement is not substantially influenced by the hyperlipemia. Because the Osmm will be 290 mmol/kg H2O, the osmolar gap will be 290 – 290 = 40 mmol/kg H2O, an abnormally high value. Thus, lipid- or protein-induced pseudo-hyponatremia must be associated with an elevated osmolar gap.

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the situation in hyperglycemia-induced hyponatremia, wherein Osmgrow is increased.) The Osmgrow will be (2)(120) + 75 + 5 + 5 = 325 mmol/kg H2O; thus, the osmolar gap is 325 – 250 = 75 mmol/kg H2O, a considerably elevated level, again contrasting with the situation obtaining in hyperglycemia wherein the osmolar gap is normal. The effective osmolality is 325 – 5 = 320 mmol/kg H2O; this high value, indicative of hypotonicity, places the patient at increased risk for cerebral dehydration, rather than cerebral edema.22,23

True Hyponatremia Together With Elevated SUN Level

We have found that this situation is one of the least well understood conditions regarding the interrelationships between serum sodium, osmolality and osmolar gap, and toxicity. A patient with true hyponatremia (eg, a patient with the syndrome of inappropriate secretion of antidiuretic hormone whose serum sodium level is 120 mmol/L) might develop incidental acute renal failure. If the SUN level were to rise to 45 mmol/L (126 mg/dL), the Osmgrow would be (2)(120) + 5 + 45 = 290 mmol/kg H2O, a normal value. The Osmgrow would also be 290 mmol/kg H2O because urea’s contribution is not only measured in Osmgrow but also calculated in Osm. Thus, the osmolar gap is 0 mmol/kg H2O. The important point, frequently not appreciated, is that finding a normal Osmgrow (or even an increased Osmgrow) does not preclude an increased risk of cerebral edema from hypotonicity. Because urea is not an effective solute (see “Definitions of Terms” section, above), the effective osmolality is 290 – 45 = 245 mmol/kg H2O, an abnormally low value, which is indicative of an increased risk of cerebral edema. Thus, in our examples, both the patient with a high SUN level and the patient with a high alcohol level are hypotonic, but only the ethanol abuser has an increased osmolar gap.

Hyponatremia

This example is provided for contrast. If the patient has a serum sodium concentration of 160 mmol/L, the Osmgrow is (2)(160) + 5 + 5 = 330 mmol/kg H2O; the Osmgrow will be the same, and therefore, the osmolar gap is 0 mmol/kg H2O. The effective osmolality will be 330 – 5 = 325 mmol/kg H2O, which is abnormally increased. Thus, a hyponatremic patient is always both hyperosmolar and hypertonic.22,23, there is no such thing as “pseudohyponatremia.”

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Corresponding author: James R. Oster, MD, Medical Service (111), Veterans Affairs Medical Center, 1201 NW 16th St, Miami, FL 33125.