Indices of Serum Tonicity in Clinical Practice

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Abstract: Although disturbances of serum tonicity (effective osmolality) may have dire consequences, only surrogate indices of tonicity are available in practice. This report identifies the appropriate index for expressing clinical states of dystonicity. Serum sodium concentration ($[Na]_S$) and osmolality ($[Osm]_S$) may be incongruent. When the tonicity state shown by $[Osm]_S$ is higher than $[Na]_S$ and the difference between the 2 indices is caused by an excess of solute that distributes in total body water, tonicity is described by $[Na]_S$. When this difference results from a gain of solute with extracellular distribution like mannitol or a decrease in serum water content, causing a falsely low measurement of $[Na]_S$, $[Osm]_S$ accurately reflects tonicity. Two indices of tonicity are applicable during hyperglycemia: the tonicity formula ($2 \cdot [Na]_S + [Glucose]_S/18$) and the corrected $[Na]_S$ ($[Na]_S$ corrected to a normal $[Glucose]_S$ using an empirically derived coefficient). Clinicians should understand the uses and limitations of the tonicity indices.

Key Indexing Terms: Serum tonicity; Effective osmolality; Serum sodium concentration; Serum osmolality; Hyperglycemia. **[Am J Med Sci 2015;349(6):537–544.]**

Homeostasis of proper mammalian cell volume, particularly brain cells, is critical for cell survival and proper function. Complex processes and mechanisms are required to maintain optimal cell volume,[1] and in clinical practice, the major challenge is to monitor and adjust the tonicity of body fluids.[2–4]

The tonicity or effective osmolality of a biologic fluid or infusion solution is defined as its property of maintaining or altering the volume of cells suspended in it. This occurs through fluid movement into or out of these cells induced by osmotic pressure differences across the cell membrane.[5] Solutions that cause osmotic exit of fluid from cells are designated hypertonic, whereas those causing osmotic entry of fluids into cells are called hypotonic. An isotonic solution is one that does not cause any net fluid transfer between the 2 major body fluid compartments. In the steady state, tonicity is nominally the same in blood, interstitial compartment and intracellular compartment.[6] Consequently, serum tonicity reflects the tonicity of all major body fluid compartments. Because severe clinical consequences, including death, can develop in hypertonic[2,7,8] or hypotonic[5,9–12] states, it is imperative that measurements and estimates of serum tonicity are accurate.

The tonicity of a solution is measured directly by suspending cells, usually red blood cells, in the solution of interest and recording the changes in their volume by rapid sequence imaging techniques.[13] Because this method requires expensive equipment and technical expertise, its use is usually limited to research studies. An example of rapid photographic recording of cell volume changes is the study that established aquaporin 1 as a water channel in cell membranes.[14] Normal Xenopus oocytes do not express aquaporin 1 and do not change their volume after suspension in nonisotonic solutions. However, Xenopus oocytes expressing aquaporin 1 after intracellular injection of aquaporin 1 messenger RNA and incorporation of aquaporin 1 into their cell membranes do swell after suspension in hypotonic solutions.[13]

In clinical practice, serum tonicity is estimated by surrogate indices including biochemical measurements that have general application and formulas that combine measurements and are applied only in a specific state of dystonicity. Both categories of indices may have substantial margins of error in certain clinical states and therefore limitations in their applications. This report addresses the uses and limitations of the surrogate indices of serum tonicity. The authors' aim is to assist clinicians managing patients with dystonicity in the selection of the proper index for evaluating the tonicity at presentation, monitoring changes in tonicity during treatment and investigating the causes of deviation of tonicity from its intended target value during treatment. The authors will use examples from the literature to illustrate the concepts presented. Representative cases are reported below.

Representative Cases

Patient 1

A woman had the following serum chemistries at admission with protracted vomiting and hypotension: Glucose ($[Glucose]_S$) 63 mg/dL, urea nitrogen ([SUN]) 7 mg/L, sodium ($[Na]_S$) 116 mmol/L and osmolality ($[Osm]_S$) 314 mOsm/kg. Serum osmolarity calculated by equation (1) (see equation 1 below) was 238 mOsm/L, and osmolal gap, the difference between $[Osm]_S$ and serum osmolality,[15] was 78 mOsm/L. The large osmolal gap was due to a serum ethanol level of 322 mg/dL or 70 mmol/L.[16]

Patient 2

A man with severe brain injury and anuria after a motor vehicle accident was transferred promptly from one hospital to a regional medical center. Laboratory values on admission to the 2nd hospital included $[Glucose]_S$ 82 mg/dL, [SUN]25 mg/dL, $[Na]_S$ 118 mmol/L and $[Osm]_S$ 338 mOsm/kg. Calculated serum osmolarity (equation (1) was 249.5 mOsm/L and osmolal gap was 88.5 mOsm'L. The large osmolal gap was caused by infusion of hypertonic mannitol in the 1st hospital.

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Patient 3

A patient on chronic peritoneal dialysis had the following serum biochemistry values at presentation with hyperglycemia: $[Glucose]_S$ 1,240 mg/dL, $[Na]_S$ 103 mmol/L, [SUN] 141 mg/dL, measured osmolality 331 mOsm/kg and calculated osmolarity (equation (1)) 325.3 mOsm/L.[17]

Patient 4

A boy without the previous diagnosis of diabetes mellitus presented with severe hypotension, coma and seizures. Initial $[Glucose]_S$ was 2,226 mg/dL and $[Na]_S$ 135 mmol/L. He was infused with insulin and large volumes of saline containing potassium salts. In 4 subsequent measurements, $[Glucose]_S$ decreased progressively to 1,239 mg/dL while $[Na]_S$ increased concomitantly to 162 mmol/L.[17]

General Indices of Serum Tonicity

The general indices of serum tonicity include serum sodium concentration ($[Na]_S$) and serum osmolality ($[Osm]_S$). Normally, sodium salts, which are effectively limited to the extracellular compartment, account for more than 90% of the serum tonicity. Alterations in $[Na]_S$ reflect changes in serum tonicity with certain notable exceptions which will be discussed later. It should be stressed that the state of tonicity is the only information provided by measuring $[Na]_S$.

$[Osm]_S$ is measured by one of the colligative properties of the serum, usually depression of its freezing point. The information provided by $[Osm]_S$ includes serum tonicity and the presence of abnormalities in serum water content or of additional solutes not normally present in significant amounts in serum. These last 2 categories of disturbances require comparison of $[Osm]_S$ with the sum of the osmotic equivalents of $[Na]_S$ and other solutes normally found in the serum. Table 1 shows the possible combinations of $[Na]_S$ and $[Osm]_S$ and the serum tonicity state denoted by each combination. The 2 indices indicate the same state of tonicity in the 1st 3 rows of Table 1. In the last 3 rows of this table, $[Na]_S$ indicates a state of tonicity lower than $[Osm]_S$.

Agreement Between $[Na]_S$ and $[Osm]_S$

Diagnosis of the state of serum tonicity is straightforward when the direction of change from normal is the same for both indices. Without exception, low $[Na]_S$ and low $[Osm]_S$ indicate hypotonicity, whereas normal $[Na]_S$ and normal $[Osm]_S$ denote isotonicity. When $[Na]_S$ is elevated, the condition of hypertonicity obtains. The evaluation of serum tonicity is more complicated when there is a discrepancy in the direction of the changes of the 2 indices.

TABLE 1. Sodium concentration, osmolality and tonicity status of the serum

$[Na]_S$	$[Osm]_S$	Serum tonicity status
↔	↔	Isotonicity
↓	↓	Hypotonicity
↑	↑	Hypertonicity
↓	↔	Isotonicity or hypotonicity
↔	↑	Isotonicity or hypertonicity
↓	↑	Isotonicity, hypotonicity or hypertonicity

$[Na]_S$, serum sodium concentration; $[Osm]_S$, serum osmolality.

Disagreement Between $[Na]_S$ and $[Osm]_S$

$[Osm]_S$ is always elevated when $[Na]_S$ is elevated but indicates a different state of tonicity from $[Na]_S$ when it is elevated and $[Na]_S$ is low or normal. This is shown in the last 3 rows of Table 1. The difference between the 2 tonicity indices is caused by either a laboratory artifact or the presence in the serum of excessive amounts of solutes other than sodium salts. Evaluation of the state of tonicity in this instance requires knowledge of the source of the laboratory artifact and whether the excess solute is distributed in total body water or in the extracellular compartment. Solutes that cross cell membranes distribute equally between intracellular and extracellular compartments and are therefore distributed in total body water. These solutes do not produce water shifts between these compartments and therefore do not contribute to serum tonicity. Solutes that do not cross cell membranes distribute only in the extracellular fluid compartment and cause internal osmotic fluid shifts. Figure 1 shows the effects on the distribution of body water between the intracellular and extracellular compartments and on serum osmolality and tonicity of gains in solute with extracellular or body water distribution. Figure 2 guides the interpretation of serum tonicity data when $[Na]_S$ and $[Osm]_S$ values do not agree.

Normal $[Osm]_S$ and Low $[Na]_S$

The combination of normal $[Osm]_S$ and low $[Na]_S$ is indicative of either isotonicity or hypotonicity. Isotonicity is present in states associated with a decrease in serum water content. The fractional water content of the serum is reduced by excess lipids or proteins. In subjects with hyperlipidemia or hyperproteinemia, measurement of $[Na]_S$ by means of flame photometry or use of the indirect ion-specific electrode (ISE) results in a systematic underestimation of the concentration of sodium in serum water because the aqueous volume of the sample is overestimated.[5] In this case, pseudohyponatremia is present and $[Na]_S$ incorrectly suggests hypotonicity. The most appropriate way to assess tonicity is by means of $[Osm]_S$ or $[Na]_S$ measured by direct ISE.[5] However, direct ISE is not available in many hospital laboratories. The verification of isotonicity requires measurement of serum lipids and proteins in cases of normal $[Osm]_S$ and low $[Na]_S$.

The 2nd category of isotonicity that occurs when $[Osm]_S$ is normal and $[Na]_S$ is low results from the administration of solutions containing solutes, other than sodium salts, with extracellular distribution. The tonicity of the added solution determines the change in serum tonicity. Gain of an isotonic solution will produce isotonic hyponatremia by dilution of extracellular sodium. This phenomenon has been seen in patients undergoing surgical procedures, such as transurethral prostatectomy, requiring irrigation of the operative field with large volumes of an irrigant solution containing 5% mannitol, which has an osmolality of 275 mOsm/kg. Entry into the blood compartment of large volumes of this solution through the exposed vasculature causes hyponatremia by dilution without changing the cell volume. $[Osm]_S$, which remains normal, is the appropriate indicator of tonicity, whereas the low $[Na]_S$ incorrectly suggests hypotonicity.[5] Entry into the blood compartment of one of the other irrigant solutions that were used for the same purpose, 1.5% glycine with an osmolality of 200 mOsm/kg and 3% sorbitol with an osmolality of 165 mOsm/kg, produces hypotonicity and hyponatremia. $[Osm]_S$ is the proper indicator of tonicity in this instance, whereas hyponatremia overestimates the degree of hypotonicity.

Hypotonicity associated with the combination of normal or elevated $[Osm]_S$ and low $[Na]_S$ is encountered when there is