The Paradox of Sodium's Volume of Distribution

Why an Extracellular Solute Appears to Distribute Over Total Body Water

When treating hyponatremia, one must know how sodium distributes in the body in order to calculate how much sodium is needed to raise the serum sodium concentration by a desired amount. Most clinicians recognize that while sodium is primarily restricted to the extracellular space it appears to distribute over total body water.[1] However, the reason for this seeming paradox is not self-evident. The standard explanation is that the osmotic effect of added sodium draws water out of cells into the extracellular space.[2-5] But is this the whole story? If so, one would predict that other solutes restricted to the extracellular space (eg, mannitol) would also appear to distribute over total body water. However, such is not the case. Therefore, it is our purpose to review why sodium appears to distribute over a different volume than the anatomic space in which it resides. We further show why solutes restricted to the same body spaces may appear to distribute over widely varying volumes.

VOLUME OF DISTRIBUTION

Consider a beaker containing an unknown volume of pure water. If a known amount of solute (A) is added to the beaker, it will dissolve and distribute evenly throughout the total volume of water. This space to which the added solute is confined is called its volume of distribution (VD)[1]; it may be determined by dividing A by its final concentration (Ac):

$$VD = A/Ac \tag{1}$$

If, instead of pure water, the beaker had initially contained some amount of A, the calculation of A's volume of distribution would be modified slightly; in this case the new A added would be divided by the increment in its concentration (ΔAc), rather than its final absolute value:

$$VD = \text{Added } A/\Delta Ac \tag{2}$$

In these simple situations, A's volume of distribution is the same as the volume of water in the beaker.

On the other hand, knowing a solute's volume of distribution allows one to calculate how much of that solute would have to be added to achieve a desired increment in its concentration. For example, to raise the sodium concentration of 10 L of a 10 mmol/L sodium solution to 15 mmol/L, the amount of sodium needed (A) can be calculated by multiplying its volume of distribution by the desired increment in concentration (ΔAc):

$$A = \Delta Ac \times VD = (15\text{ mmol/L-}10\text{ mmol/L}) \times 10\text{ L} = 50\text{ mmol}$$

APPARENT VOLUME OF DISTRIBUTUION

In contrast to the beaker, in vivo many solutes do not distribute homogeneously throughout body water and may be totally or partially restricted to various body spaces.[6] But, regardless of a solute's actual anatomic location, its volume of distribution is still calculated as if it were uniformly distributed in a beaker of water by dividing the net amount added (the amount added minus the amount excreted and/or metabolized) by the increment in its steady-state serum concentration. The virtual volume so calculated is sometimes called the apparent volume of distribution (aVD) of the solute to emphasize that it frequently differs from the actual anatomic space in which the solute resides[7-9]:

$$aVD = nA/\Delta Ac \tag{3}$$

where nA is the net amount of solute added and ΔAc the change in its serum concentration.

As already noted, while sodium is primarily restricted to the extracellular space, it appears to distribute throughout total body water; ie, sodium's apparent volume of distribution is total body water. Thus, if one wishes to increase the serum sodium concentration by adding sodium, in order to calculate the amount of sodium needed, the desired increment in sodium concentration must be multiplied by total body water and not extracellular volume.[2-4] What accounts for this paradox?

SODIUM'S VOLUME OF DISTRIBUTION

To understand sodium's behavior in the body, it is important to first review the basic anatomy of body fluids (Fig 1). Sodium salts make up the great majority of extracellular solute, while potassium salts account for most intracellular solute.[10] Since there is about twice as much intracellular solute as extracellular solute (on an osmolar basis), and because cell membranes are freely permeable to water (thereby ensuring equality of intracellular and extracellular osmolarity), about two thirds of total body water is intracellular and one third is extracellular.[11]

If additional solute, which is effectively excluded from the cells (such as sodium), is added to the extracellular space, it will cause a transient osmotic disequilibrium across the cell membrane; water will then move from the intracellular space into the now more concentrated extracellular space, until osmotic equilibrium is restored.[1] It is this shift in cellular water that is often given as the explanation for why sodium appears to distribute throughout total body water.[2-5] However this explanation is not sufficient.

Consider an anephric person (to eliminate the effect of urinary excretion) with a serum sodium (and cellular potassium) concentration of 140 mmol/L, an extracellular volume (ECV) of 14 L, and an intracellular volume (ICV) of 28 L (Fig 2). Suppose sodium's apparent volume of distribution is unknown; if 280 mmol of sodium are added to the ECV, what is the final serum sodium concentration?

To answer this, sodium is assumed to be restricted to the ECV; the solute content and concentration of the ECV in-

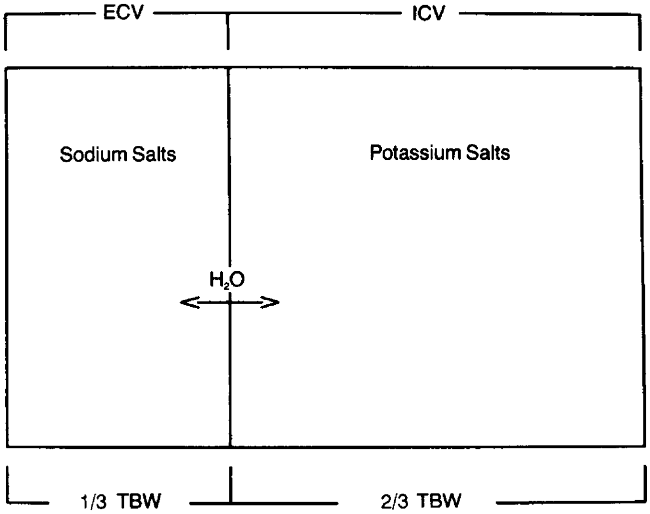

Fig 1.—Normal division of total body water (TBW) into extracellular (ECV) and intracellular (ICV) volumes. The horizontal arrow shows that water moves freely between these spaces, thereby ensuring equality of extracellular and intracellular osmolarity.

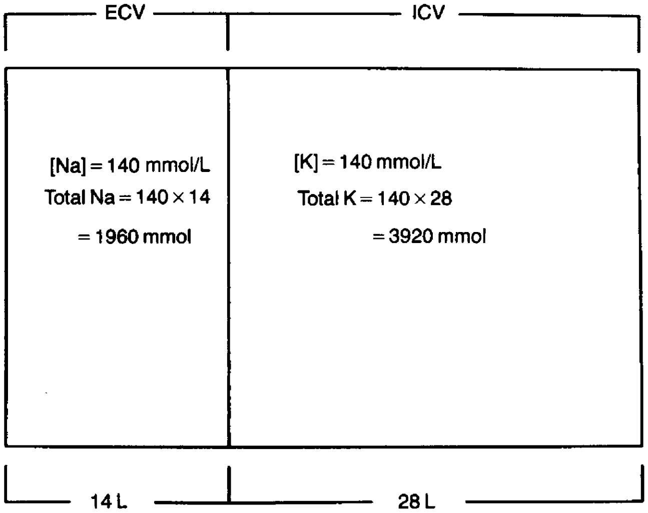

Fig 2.—Normal extracellular (ECV) and intracellular (ICV) volumes and composition of a hypothetical person weighing 70 kg. The ratio of extracellular sodium (Na) salts to intracellular potassium (K) salts is 1:2; these salts account for the great majority of osmotically active solute and are present in equal concentrations. For simplicity, only the cations are shown.

creases, thus causing an osmotic disequilibrium across the cell membrane. Since there is no change in total intracellular solute, osmotic equilibrium must be restored by a shift of cellular water to the extracellular space, which expands the ECV and contracts the ICV. At equilibrium, intracellular and extracellular total solute concentrations (ie, osmolarity) are equal:

$$\text{New Total Extracellular Solute/New ECV} = \text{Total Intracellular Solute/New ICV} \tag{4}$$

This relationship can be used to calculate the volume of water shifted (X) from the ICV to the ECV. Sodium and potassium can be substituted for extracellular and intracellular solute, respectively, in equation 4, since extracellular and intracellular solute is composed primarily of sodium and potassium salts, and the anions simply cancel out. In the example:

$$[(140\ \text{mmol/L} \times 14\ \text{L}) + 280\ \text{mmol}]/(14\ \text{L} + X) = 140\ \text{mmol/L} \times 28\ \text{L}/(28\ \text{L} - X)$$

where $X = 1.27$ L, the volume of water shifted. At this new equilibrium (Fig 3), the final sodium concentration is the new total sodium content in the ECV divided by the new ECV:

$$[(140\ \text{mmol/L} \times 14\ \text{L}) + 280\ \text{mmol}]/15.27\ \text{L} = 146.67\ \text{mmol/L}$$

What then is the apparent volume of distribution (*aVD*) of sodium? The addition of 280 mmol of sodium increased the sodium concentration by 6.67 mmol/L. Therefore, according to equation 3, the *aVD* for sodium equals:

$$280\ \text{mmol}/(6.67\ \text{mmol/L}) = 42\ \text{L}$$

which is identical to total body water in our example. But in reality, sodium remained in the extracellular space.

This seeming contradiction is understood when one looks at how the final serum sodium concentration was arrived at. It is, in effect, the sum of two sodium concentrations: that of sodium originally present in the extracellular space and that of the newly added sodium (Fig 3). The concentration of the sodium originally present was actually reduced by the inflow of cellular water, which expanded the extracellular space. Thus, the concentration of the original sodium is now the original sodium content divided by the new ECV:

$$140\ \text{mmol/L} \times 14\ \text{L}/15.27\ \text{L} = 128.33\ \text{mmol/L}$$

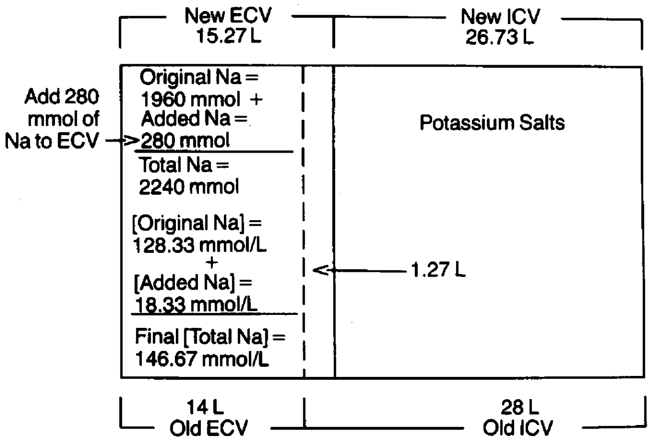

Fig 3.—The effect of adding sodium (Na) to the extracellular space on the serum sodium concentration and the distribution of water in a hypothetical anephric subject. Note the shift in cellular water to the extracellular space; this shift dilutes the sodium originally present (from 140 to 128.33 mmol/L) and thus blunts the increase in the final total sodium concentration. ECV indicates extracellular volume; ICV, intracellular volume.

The concentration of the added sodium is:

$$280\ \text{mmol}/15.27\ \text{L} = 18.33\ \text{mmol/L}$$

Hence, the final sodium concentration is the sum of the above two concentrations:

$$128.33\ \text{mmol/L} + 18.33\ \text{mmol/L} = 146.67\ \text{mmol/L}$$

which is identical to the value calculated assuming a volume of distribution for sodium of total body water.

These calculations show that although primarily restricted to the extracellular space, sodium appears to distribute over a much larger volume for two reasons. First, in line with the classic explanation, the shift in cellular water expands the ECV. However, this factor alone makes only a small contribution to sodium's large apparent volume of distribution. Also important is the often neglected but critical fact that sodium is

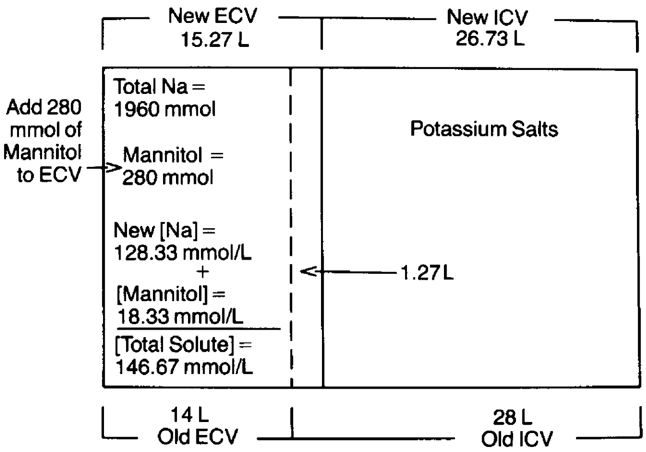

Fig 4.—The effect of adding mannitol to the extracellular space of the same hypothetical person depicted in Fig 2. The water shift is identical to that in Fig 3. But because there is no initial mannitol to dilute, mannitol increases its own concentration to a greater degree than does sodium (Na). ECV indicates extracellular volume; ICV, intracellular volume.

already present in the ECV in high concentration and this original sodium is diluted by the shift of cellular water, thereby blunting the increase in the final total sodium concentration.[12]

MANNITOL'S VOLUME OF DISTRIBUTION

Like sodium, mannitol remains in the extracellular space and draws water out of the intracellular space.[11] Consider the same hypothetical anephric person to whom an osmotically identical amount of mannitol (instead of sodium) has been added—what is the final mannitol concentration and what is its apparent volume of distribution? (It should be noted here that mannitol is not a salt. Therefore, to deliver truly equiosmotic amounts of mannitol and sodium one must give twice as much mannitol [on a molar basis] to account for the osmotic effect of sodium's accompanying anion. For the sake of simplicity, we have chosen to ignore the anions; therefore, in the examples the amount of sodium and mannitol given is the same. This simplification in no way affects the validity of our conclusions.)

The shift of cellular water will be exactly the same as in the sodium example, since an equiosmotic amount of solute was added (Fig 4). Therefore, in view of its true behavior (which is similar to sodium) one might initially think that mannitol would, like sodium, have an apparent volume of distribution of total body water. But in fact it does not; indeed, unlike sodium, its apparent volume of distribution is equal to the new ECV (ie, the original ECV plus the cellular water shift). This is explained by the fact that in contrast to sodium, which is always present in the extracellular space in high concentration, mannitol is not; hence, unlike sodium, there is no initial mannitol to dilute. Mannitol is analogous to the added sodium in the first example and its concentration would be:

$$280 \text{ mmol}/15.27 \text{ L} = 18.33 \text{ mmol/L}$$

which is the same as the concentration of added sodium in case 1.

This example again shows that the cellular water shift alone cannot explain the difference between sodium's apparent and true volumes of distribution. Note that with both sodium and mannitol this shift was identical. Yet, despite adding equiosmotic amounts, sodium increased its own concentration by only about a third of the increase in mannitol concentration. Once again, the key point is that sodium was already present (and this sodium was diluted), while mannitol was not.

Nevertheless, it should be noted that despite their differing apparent volumes of distribution, sodium and mannitol both increased the *total solute* concentration (ie, osmolarity) by the same amount (Figs 3 and 4). Thus, in the mannitol example, although there were 18.33 mmol of new solute (ie, mannitol) per liter of extracellular fluid, the sodium concentration was depressed by the shift of water to 128.33 mmol/L; therefore, the new total solute concentration is 146.67 mmol/L, just as in the sodium example.

COMMENT

The apparent volume of distribution of a solute confined to the extracellular space is a function of its initial plasma concentration; indeed it has been shown that the greater the initial contribution of an extracellular solute to the total effective osmolarity, the closer its apparent volume of distribution is to total body water.[12] Thus sodium, which (with its anions) accounts for almost all the extracellular solute, appears to distribute over total body water. Chloride, although also essentially restricted to the extracellular space, is initially present in lower concentration than sodium and, therefore, has a smaller apparent volume of distribution.[12] When a solute is restricted to the extracellular space but is not initally present (eg, mannitol), its volume of distribution is the new extracellular volume.

Aaron Spital, MD
Division of Nephrology, B2N
The Francis Scott Key Medical Center
4940 Eastern Ave
Baltimore, MD 21224

Richard D. Sterns, MD
Division of Nephrology
University of Rochester School of Medicine
601 Elmwood Ave
Rochester, NY 14642

We wish to thank Robin Spital, PhD, Gary Briefel, MD, and Anis Y. Akrawi, MD, for their helpful comments.

Reprints available.

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