# New Approach to Disturbances in the Plasma Sodium Concentration

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**Hyponatremia and hypernatremia are among the most common electrolyte disorders. Since the plasma sodium level is determined by the ratio between the total quantity of effective solutes (primarily sodium and potassium salts) and the total body water, abnormalities in the plasma sodium level must be produced by a change in one or more of these parameters. In most patients, alterations in body water are of primary importance because the plasma sodium level is normally regulated by changing water intake and water excretion. Measurement of free water excretion has traditionally been calculated by using a formula that includes the urine osmolality. However, urea is a major urinary solute but does not contribute to regulation of the plasma sodium level, since it is an ineffective osmole. As a result, urinary solute excretion is best expressed as $2 \times U_{Na+K}$. Making this important correction allows solute and water intake and excretion to be compared, thereby leading to a better understanding of both the development and correction of disturbances in the plasma sodium level.**

Hyponatremia and hypernatremia are among the most common electrolyte disorders. Nevertheless, errors in diagnosis and management may occur because of misconceptions about the meaning of the plasma sodium concentration and the factors that regulate it. This review discusses these concepts with particular emphasis on the importance of the relationship between solute and water balance and a new approach to the measurement of urinary water excretion.

## DETERMINANTS OF THE PLASMA SODIUM LEVEL

Sodium salts, primarily chloride and bicarbonate, are the major solutes in plasma, with glucose, urea, and other ions normally playing a much smaller role. As a result, the plasma sodium concentration ($P_{Na}$) is the primary determinant of the plasma osmolality ($P_{osm}$), since the latter is a function of the number of solute particles per liter of plasma. This relationship can be expressed by the following equation [1]:

$$P_{OSM} \cong \times P_{Na} \quad (1)$$

($2 \times P_{Na}$ is used to account for the anions accompanying sodium.)

The plasma osmolality is also roughly equal to total body osmolality because almost all of the body water in the extracellular and intracellular compartments is in osmotic equilibrium. The total body osmolality is equal to the ratio of total body solute to total body water. Thus,

$$P_{OSM} = \text{Total body osmolality} = \frac{\text{Extracellular + intracellular solutes}}{\text{Total body water}} \quad (2)$$

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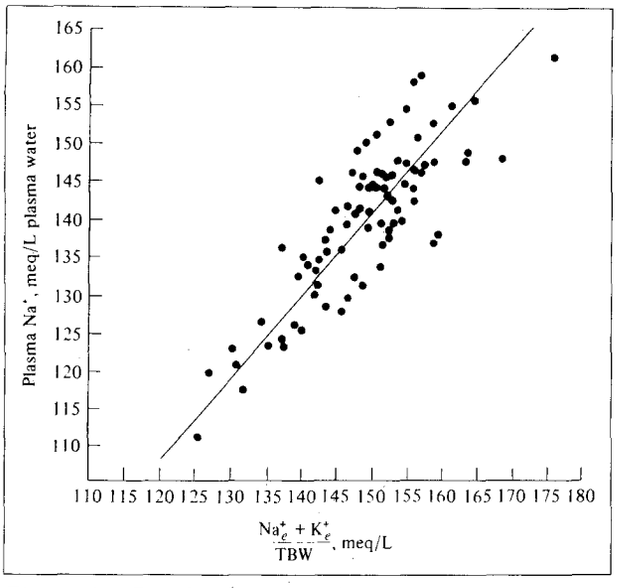


***Figure 1.*** *Relation between the plasma water sodium concentration and the ratio of exchangeable sodium ion ($Na_e^+$) plus exchangeable potassium ion ($K_e^+$) to total body water (TBW). Each point represents a measurement from a different patient. (Adapted with permission from [2].)*

Since sodium and potassium salts are the primary extracellular and intracellular solutes, respectively, the last equation can be converted to:

$$P_{OSM} \cong \frac{2 \times Na_e + 2 \times K_e}{\text{Total body water}} \quad (3)$$

where $Na_e$ and $K_e$ refer to the "exchangeable" quantities of sodium and potassium and the multiple 2 again accounts for the accompanying anions. The exchangeable portion is used because about 30 percent of the body sodium and a small fraction of the body potassium are bound in areas such as bone where they are osmotically inactive. If equations 1 and 3 are now combined [2]:

$$P_{Na} \cong \frac{Na_e + K_e}{\text{Total body water}} \quad (4)$$

This relationship is depicted graphically in **Figure 1.**

Although it is not surprising that changes in either sodium or water balance can influence the plasma sodium concentration, the effect of potassium can also be clinically important. If potassium is lost from the extracellular fluid due to gastrointestinal or renal losses, the extracellular potassium concentration will fall. In this setting, intracellular potassium will move passively into the extracellular fluid. To maintain electroneutrality, sodium (and to a lesser degree hydrogen) will enter the cells, thereby lowering the plasma sodium concentration. This sequence will not generally lead to persistent hyponatremia because the initial fall in the plasma osmolality will shut off the release of antidiuretic hormone, resulting in increased water excretion, which will return the plasma sodium concentration to normal (see later). If, however, antidiuretic hormone secretion cannot be reduced, then potassium depletion can lower the plasma sodium concentration. In some patients with diuretic-induced hyponatremia, for example, volume depletion stimulates the release of antidiuretic hormone, and concurrent potassium depletion may contribute to the fall in the plasma sodium concentration [3,4]. In this situation, solely administering potassium can raise the plasma sodium concentration toward normal [4]. Potassium supplements can also elevate the plasma sodium concentration in normokalemic patients, although this is not recommended because of the associated elevation in the plasma potassium concentration [5].

In addition to sodium, potassium, and water, high extracellular concentrations of other effective solutes such as glucose (in uncontrolled diabetes mellitus) or mannitol (given to treat cerebral edema or oliguria) can also affect the plasma sodium concentration. In these settings, the extra solute raises the plasma osmolality. This causes water to move out of the cells down an osmotic gradient, lowering the plasma sodium concentration by dilution [6,7].

In comparison, urea is without effect on the plasma sodium concentration, since it can easily cross the cell membrane. Thus, a high plasma urea concentration (as occurs in renal failure) is associated with urea equilibration between the extracellular and intracellular fluids. There is no change in sodium or water distribution and therefore no change in the plasma sodium concentration.

## REGULATION OF THE PLASMA SODIUM LEVEL

The plasma osmolality and plasma sodium concentration are regulated by osmoreceptors in the hypothalamus that affect thirst and the release of antidiuretic hormone [8]. A water load, for example, lowers the plasma osmolality and plasma sodium concentration. This inhibits antidiuretic hormone release, thereby reducing collecting tubule water reabsorption, lowering the urine osmolality, and allowing the excess water to be excreted. In contrast, water loss due to sweating on a hot day leads to elevations in the plasma osmolality and plasma sodium concentration. This enhances both thirst and the secretion of antidiuretic hormone. The combination of increased intake and reduced water excretion (high urine osmolality) results in water retention and a fall in the plasma osmolality and plasma sodium concentration toward normal.

These examples illustrate that the plasma sodium concentration is maintained by changes in water, not sodium balance. The renin-angiotensin-aldosterone and sympathetic nervous systems, which are important in volume

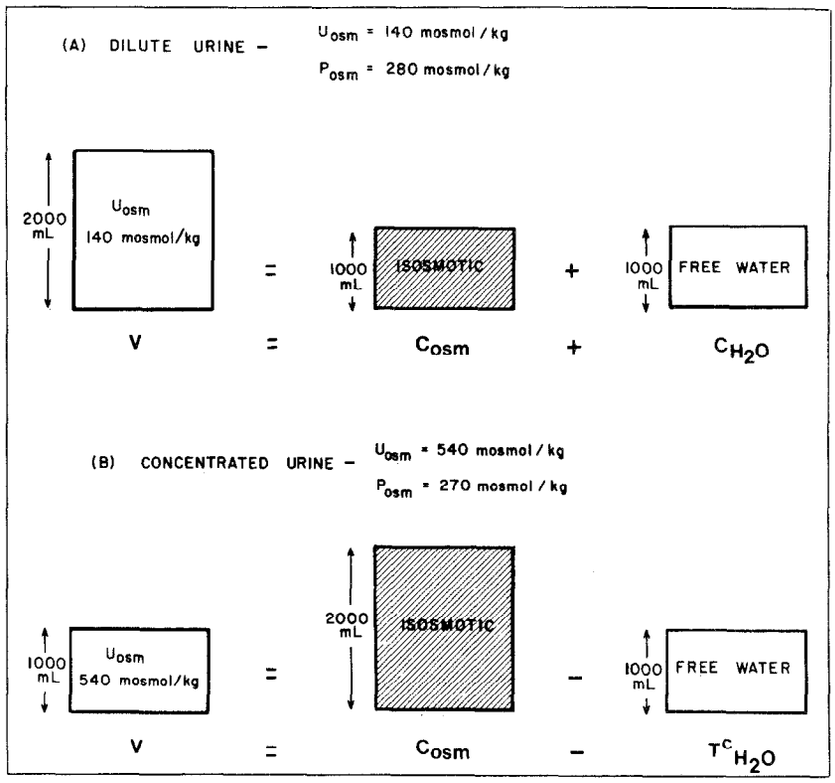


***Figure 2.*** *Block diagrams showing the relation between the urine volume (V) and its two components: one containing all of the urinary solute in a solution that is isosmotic to plasma (the osmolar clearance, $C_{osm}$) and one consisting of free water that has been generated (the free water clearance, $C_{H_2O}$) or reabsorbed (the free water reabsorption, $T^C_{H_2O}$) to attain the final urine osmolality ($U_{osm}$). See text for details. $P_{osm}$ = plasma osmolality.*

regulation and sodium excretion, do not play an important role in the control of the plasma sodium concentration [9,10].

## MEASUREMENT OF RENAL WATER EXCRETION

Regulation of the plasma sodium concentration can be more completely understood by a review of how to measure the amount of free water excreted or retained by the kidney.

**Traditional Theory.** As antidiuretic hormone secretion varies in the face of changing solute and water intake, the quantitative ability of the kidney to excrete or retain water can be calculated. Suppose a patient has the following laboratory data: urine volume = 2,000 ml per day; urine osmolality = 140 mOsmol/kg; plasma osmolality = 280 mOsmol/kg. It can be appreciated that the urine osmolality is one half that of the plasma. In this setting, the 2,000 ml of urine (containing a total of 280 mOsmol of solute) can be viewed as having two components (**Figure 2A**): (1) 1,000 ml containing all the solute in an isosmotic solution (280 mOsmol in 1,000 ml); (2) 1,000 ml containing solute-free water, which has been generated from initially isosmotic urine by sodium chloride reabsorption without water in the loop of Henle and distal nephron (in the relative absence of antidiuretic hormone). The latter is called the free water clearance ($C_{H_2O}$) and the former the osmolar clearance ($C_{osm}$). The osmolar clearance represents the volume of plasma cleared of the solute it contains by urinary excretion and can be calculated from the general formula for clearance: $C_{osm} = U_{osm}\ V/P_{osm}$. Thus,

$$\text{Urine volume (V)} = C_{OSM} + C_{H_2O} \quad (5)$$

$$C_{H_2O} = V - C_{OSM} \quad (6)$$

$$= V - \frac{U_{OSM}\,V}{P_{OSM}}$$

$$= V\left(1 - \frac{U_{OSM}}{P_{OSM}}\right) \quad (7)$$

If the aforementioned laboratory values are inserted into the formula:

$$C_{H_2O} = 2{,}000\left(1 - \frac{140}{280}\right) = 1{,}000 \text{ ml/day} \quad (8)$$

Similar considerations apply to the excretion of a concentrated urine. Suppose the following laboratory data are obtained: urine volume = 1,000 ml per day; urine osmolality = 540 mOsmol/kg; plasma osmolality = 270 mOsmol/kg. The excretion of 1,000 ml of urine with an osmolality twice that of the plasma can be viewed as being derived from 2,000 ml of isosmotic urine (the

osmolar clearance) from which 1,000 ml of free water has been reabsorbed in the medullary collecting tubule in the presence of antidiuretic hormone (the free water reabsorption or $T^c_{H_2O}$). Thus (**Figure 2B**),

$$V = C_{OSM} - T^c_{H_2O} \quad (9)$$

$$T^c_{H_2O} = C_{OSM} - V$$

$$= V\left(\frac{U_{OSM}}{P_{OSM}} - 1\right) \quad (10)$$

(Notice that $T^c_{H_2O} = -C_{H_2O}$. In other words, free water reabsorption is the opposite of free water excretion.) Using the aforementioned values:

$$T^c_{H_2O} = 1{,}000\left(\frac{540}{270} - 1\right) = 1{,}000 \text{ ml/day} \quad (11)$$

**Electrolyte-Free Water Reabsorption.** The traditional formulas for free water clearance and reabsorption describe urinary water excretion in relation to total solutes. This concept, however, is somewhat erroneous when viewed in terms of the regulation of the plasma osmolality and plasma sodium concentration. As just described, the plasma sodium concentration is determined by the relationship between sodium, potassium, and total body water (Figure 1). Although urea does not contribute to this relationship, it is one of the major urinary solutes along with sodium and potassium salts. To the degree that urea is lost in the urine, the plasma urea concentration will fall. This will cause urea to diffuse out of cellular stores but will not affect the plasma sodium concentration. To more accurately determine the effect of urinary solute and water excretion on the plasma sodium concentration, equation 10 should be amended in the following ways [11]: (1) Two times the (urine sodium + urine potassium) should be substituted for the urine osmolality; (2) Two times the plasma sodium should be substituted for the plasma osmolality. When these changes are made, the more accurate formula for "electrolyte-free water reabsorption" ($T^c_{H_2O}$) can be derived [11]:

$$\overset{e}{T}{}^c_{H_2O} = V\left(\frac{U_{Na+K}}{P_{Na}} - 1\right) \quad (12)$$

Although urea is omitted from this equation as an ineffective solute, it may, as any solute will, obligate urinary water loss (which would tend to raise the plasma sodium concentration). This effect, however, will be accounted for in the formula by an increase in the urine volume.

The clinical importance of the difference between free water and electrolyte-free water reabsorption can be simply illustrated by returning to the aforementioned example in which the urine osmolality was 540 mOsmol/kg, the plasma osmolality was 270 mOsmol/kg, and the urine volume was 1,000 ml per day. Suppose two patients, one with heart failure and one with the syndrome of inappropriate antidiuretic hormone secretion, have the aforementioned values and a plasma sodium level of 130 meq/liter. From equation 11, both patients would be reabsorbing 1,000 ml of free water per day; the retention of this water would promote the development of hyponatremia.

Very different results, however, are obtained if the electrolyte-free water reabsorption is calculated. The patient with the syndrome of inappropriate antidiuretic hormone secretion has a urine sodium level of 90 meq/liter and a urine potassium level of 60 meq/liter. If these values are substituted in equation 12:

$$\overset{e}{T}{}^c_{H_2O} = 1{,}000\left(\frac{150}{130} - 1\right) = 150 \text{ ml/day} \quad (13)$$

Thus, the kidney is retaining only 150 ml, not 1,000 ml of water per day.

In contrast, the patient with heart failure is sodium-avid with a urine sodium level of 5 meq/liter and a urine potassium level of 45 meq/liter. In this setting:

$$\overset{e}{T}{}^c_{H_2O} = 1{,}000\left(\frac{50}{130} - 1\right) = -610 \text{ ml/day}$$

As a result, the kidney is actually excreting (not reabsorbing) 610 ml of water, tending to raise, not lower, the plasma sodium concentration. Notice that this excretion of water occurs even though the urine is concentrated. This apparently paradoxic result has occurred because most of the urinary solute is urea, not sodium and potassium. Although it is appropriate to excrete free water in this setting of mild hyponatremia, it must be emphasized that this is still an inadequate response. The low cardiac output has presumably elevated antidiuretic hormone levels via activation of volume receptors [12,13]. If antidiuretic hormone secretion were inhibited by the low plasma osmolality, the urine osmolality would fall, resulting in a marked rise in the urine output and free water excretion and normalization of the plasma sodium concentration.

These results indicate that at a given antidiuretic hormone level and urine osmolality, the kidneys are generally better able to excrete electrolyte-free water (albeit at a submaximal level) in sodium-retaining states such as heart failure than in the syndrome of inappropriate antidiuretic hormone secretion. A corollary of this conclusion is that water retention and hyponatremia should be somewhat less likely to occur in sodium-retaining states than in the syndrome of inappropriate antidiuretic hormone secretion. Although this issue has not been rigorously studied, patients with heart failure and the nephrotic syndrome generally maintain their plasma sodium concentration above 130 meq/liter despite having elevated plasma antidiuretic hormone levels similar to those in hyponatremic patients with the syndrome of inappropriate antidiuretic hormone secretion [8,12–14]. At least some of these patients were on ad lib water intake so that dietary

water restriction alone does not appear to be responsible for this difference. More severe hyponatremia in heart failure is usually seen with advanced disease in which reductions in the glomerular filtration rate and urine output as well as enhanced antidiuretic hormone secretion contribute to the inability to excrete water [15].

In summary, paying attention to sodium and potassium rather than total solute excretion leads to a more accurate assessment of water and osmolal balance. The difference between free water reabsorption and electrolyte-free water reabsorption is primarily a function of the quantity of urea in the urine. When the urine has a relatively low sodium plus potassium concentration, electrolyte-free water will continue to be excreted even though the urine osmolality may be high because of the presence of urea. For example, patients with a urea osmotic diuresis due to high protein tube feedings can become hypernatremic because of the loss of large amounts of electrolyte-free water [16]. This is an important concept, since inappropriate water loss leading to hypernatremia is usually associated with a low urine osmolality due to diabetes insipidus. This effect of urea to enhance water excretion can also be used therapeutically to raise the plasma sodium level in hyponatremic patients with the syndrome of inappropriate antidiuretic hormone secretion (see later).

## CLINICAL APPLICATIONS

The following examples illustrate how these concepts of solute and water balance can be applied in the clinical setting, particularly to patients with hyponatremia. Similar considerations apply to hypernatremia, but this disorder will not be specifically discussed.

**Diarrhea.** Diarrheal fluid is usually isosmotic to plasma [17]. At first glance, the loss of isosmotic fluid should not affect the plasma sodium concentration. However, the fecal sodium plus potassium concentration is variable, depending upon the underlying pathogenesis. In secretory diarrheas (as with cholera or hormone-secreting tumors), sodium and potassium salts make up most of the fecal osmoles, producing little direct change in the plasma sodium concentration. On the other hand, osmotic diarrheas (as with malabsorption, lactulose, or some viral enteritides) are characterized by water loss in excess of effective solute [17–19]. In this setting, the fecal sodium plus potassium concentration is usually between 30 and 110 meq/liter with the nonabsorbed solute accounting for most of the remaining osmoles [17,18].

As an example, suppose the fecal sodium and potassium concentrations are both 30 meq/liter. In this situation, the electrolyte-free water reabsorption can be calculated from the same formula just used except for the substitution of fecal for urinary electrolyte concentrations. If the plasma sodium concentration is 140 meq/liter, and the stool volume is 1,000 ml per day:

$$F^{e}_{H_2O} = V\left(\frac{F_{Na+K}}{P_{Na}} - 1\right)$$

$$= 1{,}000\left(\frac{60}{140} - 1\right) \qquad (14)$$

$$= -570 \text{ ml}$$

This loss of free water will tend to raise the plasma sodium concentration. However, other factors affecting water balance also are present in the patient with diarrhea. Fever increases water loss as sweat whereas volume depletion can stimulate both antidiuretic hormone release and thirst, resulting in water retention. If these effects balance out, as is most often the case, the plasma sodium concentration will be unchanged [20]. If, however, water intake is not increased or relatively high electrolyte feedings are given to infants, the free water losses can lead to hypernatremia [18,20,21]. Conversely, positive water balance and hyponatremia can ensue if water intake is substantially enhanced.

**Diuretic-Induced Hyponatremia.** The major way in which diuretics cause hyponatremia is by inducing volume depletion, which leads to enhanced antidiuretic hormone secretion and the retention of ingested water. Since the loop diuretics (furosemide, ethacrynic acid, and bumetanide) are the most potent, it might be expected that they would have the greatest tendency to lower the plasma sodium concentration. However, almost all reported cases of severe diuretic-induced hyponatremia have been due to a thiazide, not a loop diuretic [4,22]. Furthermore, loop diuretics can be used to help raise the plasma sodium concentration in hyponatremic patients with the syndrome of inappropriate antidiuretic hormone secretion (see later).

This preferential hyponatremia with a thiazide results from its lack of effect on urinary concentrating ability [23,24]. A concentrated urine is produced by equilibration of fluid in the collecting tubules (in the presence of antidiuretic hormone) with the hyperosmotic medullary interstitium; the latter is generated by sodium chloride reabsorption without water in the medullary ascending limb of the loop of Henle [25]. Loop diuretics interfere with this process by inhibiting sodium chloride reabsorption in the thick ascending limb; the thiazides, in contrast, act in the cortex in the distal tubule and do not affect urinary concentration [23,24]. As a result, the ability of antidiuretic hormone to increase water reabsorption in the collecting tubules and promote the development of hyponatremia is impaired by the loop diuretics but remains intact with the thiazides.

Although the inability to excrete ingested water is the primary abnormality in most hyponatremic patients, the use of a thiazide-type diuretic also represents one of the few clinical settings (other than the direct administration of sodium) in which the sum of the concentrations of sodium and potassium in the urine can exceed that in the plasma [22]. This finding results from the combination of diuretic-induced sodium and potassium excretion and the hypovo-

lemia-induced elevation in antidiuretic hormone secretion, which increases water reabsorption. The net effect is solute loss in excess of water, which can directly lower the plasma sodium concentration (from equation 4) independent of water intake. In some elderly patients with a large initial diuresis, a thiazide diuretic can lower the plasma sodium concentration by as much as 15 meq/liter within 36 hours [22].

**Syndrome of Inappropriate Antidiuretic Hormone Secretion.** The importance of considering the relationship between solute and water balance can perhaps best be illustrated by the treatment of patients with the syndrome of inappropriate antidiuretic hormone secretion. It is often stated that saline alone will produce only a transient elevation in the plasma sodium concentration in this disorder and that water restriction is the mainstay of therapy [26]. The reason for this can be appreciated from the following example. Suppose a patient with the syndrome of inappropriate antidiuretic hormone secretion has the following laboratory data: plasma sodium = 115 meq/liter; plasma osmolality = 240 mOsmol/kg; urine osmolality = 680 mOsmol/kg. If this patient is given 1,000 ml of isotonic saline (containing 154 meq of sodium and chloride or 308 mOsmol), the plasma sodium concentration will initially rise because the solution has a higher sodium concentration than the patient. However, patients with the syndrome of inappropriate antidiuretic hormone secretion are generally euvolemic and able to excrete sodium normally. As a result, the 308 mOsmol of sodium chloride will be excreted but, since the urine osmolality is relatively fixed at 680 mOsmol/kg, this additional solute will obligate the further excretion of only 453 ml of water (308 mOsmol in 453 ml equals 680 mOsmol/kg). Thus, for each liter of isotonic saline given, all of the sodium chloride will be excreted but 547 ml of the water will be retained. The net effect is water retention and a further reduction in the plasma sodium concentration.

Using several simple calculations, we can estimate how much the plasma sodium concentration should fall. If the patient were a 60 kg woman, then:

$$\text{Total body water} = 0.5 \times \text{lean body weight (kg)}$$
$$= 30 \text{ liters}$$
$$\text{Total body osmoles} = \text{total body water} \times P_{OSM}$$

If $2 \times P_{Na}$ is substituted for the plasma osmolality (from equation 1) to estimate the total body effective osmoles:

$$\text{Total body effective osmoles} = \text{total body water} \times 2\,P_{Na} \quad (15)$$
$$= 30 \times 230 = 6{,}900 \text{ mOsmol}$$

The administration of 2 liters of isotonic saline should induce 1,094 ml of water retention (547 ml/liter), raising the total body water to 31.1 liters. Since the total body effective osmole value is unchanged, the new plasma sodium concentration can be estimated by rearranging equation 15:

$$\text{New } P_{Na} = \frac{\text{Total body effective osmoles}}{2 \times \text{total body water}} \quad (16)$$
$$= 6{,}900/62.2 = 111 \text{ meq/liter} \quad (17)$$

Thus, the plasma sodium concentration should fall by about 4 meq/liter.

To effectively raise the plasma sodium concentration, sodium can be given, but the osmolality of the administered fluid must exceed that in the urine. Since the urine osmolality usually is greater than 300 mOsmol/kg in the syndrome of inappropriate antidiuretic hormone secretion, there is essentially no role for the use of isotonic saline in this disorder. However, hypertonic saline (3 or 5 percent) can be given for severe (plasma sodium concentration below 115 meq/liter) or symptomatic hyponatremia, or if fluids are to be given, even for mild to moderate hyponatremia. As an alternative, sodium chloride tablets can be given, as this supplies sodium without water.

The effect of hypertonic saline can be estimated using calculations similar to those just mentioned. If 1,000 ml of 3 percent saline is given (containing 513 meq of sodium and chloride or 1,026 mOsmol) to the patient with a urine osmolality of 680 mOsmol/kg, the 1,026 mOsmol will be excreted in 1.5 liters (1,026 mOsmol ÷ 680 mOsmol/kg = 1,500 ml), resulting in the net loss of 0.5 liter of water. This will lower the total body water to 29.5 liters, and from equation 16:

$$\text{New } P_{Na} = 6{,}900/59 = 117 \text{ meq/liter} \quad (18)$$

This 2 meq/liter rise in the plasma sodium level indicates that even 3 percent saline may not be very effective in the syndrome of inappropriate antidiuretic hormone secretion when a highly concentrated urine is being excreted. The results are substantially different, however, if a loop diuretic such as furosemide is also given to impair concentrating ability by inhibiting active sodium chloride reabsorption in the loop of Henle. Suppose furosemide lowers the urine osmolality to 300 mOsmol/kg. In this setting, the 1,026 mOsmol in 1 liter of 3 percent saline will now be excreted in 3.4 liters of urine (1,026 mOsmol ÷ 300 mOsmol/kg = 3.4 liters). This 2.4-liter negative water balance will reduce the total body water to 27.6 liters. Consequently, from equation 16:

$$\text{New } P_{Na} = 6{,}900/55.2 = 125 \text{ meq/liter} \quad (19)$$

Thus, furosemide potentiates the effect of hypertonic saline when the urine is concentrated by lowering the urine osmolality and thereby increasing the rate of water excretion [27–29]. If, however, the urine osmolality were initially 300 mOsmol/kg, furosemide would add little, since the results in equation 19 could be obtained with hypertonic saline alone. In this setting, the only indication for the use of furosemide would be to prevent possible fluid overload in a patient with a history of heart disease.

These examples illustrate that the correction of hyponatremia is dependent upon increasing the abnormally

low ratio between total body effective solute and total body water. This can be achieved in the syndrome of inappropriate antidiuretic hormone secretion by restricting water intake, administering hypertonic sodium solutions, or increasing urinary electrolyte-free water excretion. The last goal can be achieved in two ways: (1) by lowering the urine osmolality with a loop diuretic or with drugs that directly interfere with the action of antidiuretic hormone, such as demeclocycline (a tetracycline derivative) or lithium [30]; or (2) by giving urea to induce an osmotic diuresis [31].

It is recognized that the aforementioned calculations are somewhat simplified, since other sources of water intake and loss are ignored* and it is assumed that the administered sodium chloride is excreted during the same time period that the intravenous fluid is given. Nevertheless, the new steady-state will ultimately be the same even if the exogenous sodium chloride is excreted over several days. Furthermore, the concept of comparing effective solute and water intake and excretion can be applied to a same-day analysis. This can be appreciated from the following example.

A 58-year-old woman weighing 60 kg has the syndrome of inappropriate antidiuretic hormone secretion due to an oat cell carcinoma of the lung. Initial laboratory studies show a plasma sodium concentration of 102 meq/liter and a urine osmolality of 550 mOsmol/kg. Overnight, she is treated with 1,700 ml of 3 percent saline and furosemide. During this time, she excretes 3,300 ml of urine with an osmolality of 300 mOsmol/kg and sodium and potassium concentrations of 100 and 20 meq/liter, respectively. Repeated measurement shows a plasma sodium value of 123 meq/liter.

It may, at first glance, seem surprising that a negative fluid balance of only 1,600 ml would produce such a large increase in the plasma sodium concentration. The expected effect can be estimated using the calculations described before. On admission,

$$\text{Total body water} = 0.5 \times 60 = 30 \text{ liters}$$

Total body effective osmoles

$$= \text{total body water} \times 2\,P_{Na}$$

$$= 30 \times 204 = 6{,}120 \text{ mOsmol}$$

If the total body water is reduced by 1.6 liters to 28.4 liters, then from equation 16:

$$\text{New } P_{Na} = 6{,}120/56.8 = 108 \text{ meq/liter} \quad (20)$$

This value is clearly different from the measured plasma sodium concentration of 123 meq/liter. The error lies in the assumption that total body effective osmoles were unchanged. The total osmolar intake was 1,745 mOsmol* (1.7 liters at 1,026 mOsmol/liter) whereas the total excretion of sodium and potassium salts was 792 mOsmol (2 × urine [Na + K] × 3.3 liters = 792 mOsmol). Thus, there was a 953 mOsmol increase in total body effective osmoles to 7,073 mOsmol. As a result:

$$\text{New } P_{Na} = 7{,}073/56.8 = 124.5 \text{ meq/liter} \quad (21)$$

This value is essentially identical to the measured plasma sodium concentration.

**Volume Depletion.** The treatment of hyponatremia with volume depletion differs from that with the syndrome of inappropriate antidiuretic hormone secretion, since both the administered sodium and water will be retained with hypovolemia. As described before, 2 liters of isotonic saline should lower the plasma sodium concentration from 115 to 111 meq/liter in the patient with the syndrome of inappropriate antidiuretic hormone secretion (equation 17). Let us assume that a volume-depleted patient with the same initial laboratory data was given 2 liters of isotonic saline (containing 616 mOsmol of sodium chloride) but that the urine volume during this time period was only 500 ml with respective sodium and potassium concentrations of 10 and 32 meq/liter (or a total of 42 meq of effective solute, including accompanying anions, in 500 ml). In this setting, the new total body water has increased by 1.5 liters to 31.5 liters and the total body effective osmoles have increased by 574 mOsmol, from 6,900 to 7,474 mOsmol. Thus,

$$\text{New } P_{Na} = \frac{\text{Total body effective osmoles}}{2 \times \text{total body water}}$$

$$= 7{,}474/63 = 119 \text{ meq/liter} \quad (22)$$

This example illustrates that isotonic saline can be used to raise the plasma sodium concentration in patients with volume depletion. In addition to its direct effect, the administered fluid will also replenish the extracellular volume, thereby reducing antidiuretic hormone secretion. This will further correct the hyponatremia by enhancing urinary water excretion. Hypertonic saline is indicated in this situation only for severe hyponatremia.

* When oral intake is adequate, insensible water losses from the skin and respiratory tract are roughly equal to "insensible" sources of water intake [32]. The latter includes the water content of food (by weight, certain fruits and vegetables are almost 100 percent water, and meat is approximately 70 percent water) and the water derived from the oxidation of carbohydrates and fats. If intake is poor, however, insensible losses can exceed the water of oxidation by 500 ml per day or more. This is particularly true when insensible losses are enhanced due to fever or hyperventilation. In this setting, an estimate of net water loss must be included in the aforementioned calculations.

* The factors determining effective osmolar intake are similar to those affecting urinary excretion: sodium and potassium salts are of primary importance; protein intake can be ignored, since the protein will be used for anabolism or metabolized to urea, carbon dioxide, and water; glucose intake can also be ignored in normoglycemic patients, since the glucose will be stored or metabolized but will not remain osmotically active. The last consideration does not apply to hyperglycemic patients in whom calculating effective osmolar intake is not really possible, since the quantity of ingested glucose that remains osmotically active in the extracellular fluid cannot be easily determined.

## CONCLUSIONS

This review has emphasized that the plasma sodium concentration is a function of the ratio between the total body effective solutes (primarily exchangeable sodium and potassium salts) and the total body water. As a result, changes in the plasma sodium concentration can be predicted by comparing the intake and urinary excretion of sodium, potassium, and water. The traditional theory in which the total urine osmolality is used to calculate free water clearance or reabsorption is inaccurate in terms of regulation of the plasma sodium concentration and effective plasma osmolality. When there is a substantial concentration of urea in the urine, electrolyte-free water may continue to be excreted (an effect that should raise the plasma sodium concentration) despite a highly concentrated urine (which would have been thought to be associated with water retention and a reduction in the plasma sodium concentration).

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