Chapter 40

HYPERTONIC AND HYPOTONIC SYNDROMES

This chapter describes the clinical disorders that are characterized by an abnormal distribution of total body water (TBW) in the intracellular and extracellular fluid compartments. These disorders are characterized by a change in the effective osmolarity of the extracellular fluid, and many are associated with an abnormal plasma sodium concentration.

BASIC CONCEPTS

The following is a description of the forces that determine the movement of water between the intracellular and extracellular fluid compartments (1,2,3 and 4).

OSMOTIC ACTIVITY

The activity (concentration) of solute particles in a solution is inversely related to the activity (concentration) of water molecules in the solution. The solute activity in a solution is also called the *osmotic activity* and is expressed in osmoles (osm). The total osmotic activity in a solution is the sum of the individual osmotic activities of all the solute particles in the solution. For monovalent ions, the osmotic activity in milliosmoles (mOsm) per unit volume is equivalent to the concentration of the ions in milliequivalents (mEq) per unit volume. Thus, the osmotic activity in isotonic saline (0.9% sodium chloride) is as follows:

$$\begin{aligned} \text{0.9\% NaCl} &= 154\ \text{mEq Na/L} + 154\ \text{mEq Cl/L} \\ &= 154\ \text{mOsm Na/L} + 154\ \text{mOsm Cl/L} \\ &= 308\ \text{mOsm/L} \end{aligned} \qquad (40.1)$$

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Osmolarity is the osmotic activity per volume of solution (solutes plus water) and is expressed as mOsm/L. **Osmolality** is the osmotic activity per volume of water and is expressed as mOsm/kg H_2O. The osmotic activity of body fluids usually is expressed in relation to the volume of water (i.e., osmolality). However, the volume of water in body fluids is far greater than the volume of solutes, so there is little difference between the osmolality and osmolarity of body fluids. Thus, the terms osmolality and osmolarity can be used interchangeably to describe the osmotic activity in body fluids.

TONICITY

When two solutions are separated by a membrane that allows the passage of water but not solutes, the water passes from the solution with the lower

osmotic activity to the solution with the higher osmotic activity. The relative osmotic activity in the two solutions is called the effective osmolality, or *tonicity.* The solution with the higher osmolality is described as hypertonic, and the solution with the lower osmolality is described as hypotonic. Thus, the tendency for water to move into and out of cells is determined by the relative tonicity of the intracellular and extracellular fluids.

When the membrane separating two fluids is permeable to both solutes and water and a solute is added to one of the fluids, the solute equilibrates fully across the membrane. In this situation, the solute increases the osmolality of both fluids but does not change the relative tonicity of either fluid. Therefore, the water will not move from one fluid compartment to the other. An example of a solute that behaves in this manner is urea. Urea is freely permeable across cell membranes, so an increase in the urea concentration in extracellular fluid (i.e., an increase in the plasma blood urea nitrogen [BUN] increases the osmolality of the extracellular fluids but does not increase the tonicity of the extracellular fluids or cause a net movement of water out of cells. Thus, azotemia (an increase in BUN) is a hyperosmotic condition, but not a hypertonic condition.

PLASMA OSMOLALITY

The osmolality of the extracellular fluids can be measured in the clinical laboratory using the freezing point of plasma (a solution containing 1 osm/L will freeze at –1.86° C). This is the *freezing point depression* method for measuring osmolality.

The osmolality of the extracellular fluids can also be calculated using the concentrations of sodium, chloride, glucose, and urea in plasma (these are the major solutes in extracellular fluid). The calculation below uses a plasma [Na] of 140 mEq/L, a plasma [glucose] of 90 mg/dL, and a plasma [BUN] of 14 mg/dL.

$$\begin{aligned}\text{Plasma Osmolality} &= (2 \times [\text{Na}]) + \frac{[\text{Glucose}]}{18} + \frac{[\text{BUN}]}{2.8} \\ &= (2 \times 140) + \frac{90}{18} + \frac{14}{2.8} \qquad (40.2) \\ &= 290 \text{ mOsm/kg } H_2O\end{aligned}$$

The sodium concentration is doubled to include the osmotic contribution of chloride. The serum glucose and urea are measured in milligrams per deciliter, and the factors 18 and 2.8 (the atomic weights divided by 10) are used to convert mg/dL to mOsm/kg H_2O.

OSMOLAL GAP

Because solutes other than sodium, chloride, glucose, and urea are present in the extracellular fluid, the measured plasma osmolality will be greater than the calculated plasma osmolality. This osmolar gap (i.e., the difference between the measured and calculated plasma osmolality) is normally as much as 10 mOsm/kg H_2O (4,5). An increase in the osmolar gap occurs when certain toxins (e.g., ethanol, methanol, ethylene glycol, or the unidentified toxins that accumulate in renal failure) are in the extracellular fluid. Therefore, the osmolar gap has been proposed as a screening test for identifying the presence of toxins in the extracellular fluid. In the case of renal failure, the osmolar gap has been recommended as a reliable test for distinguishing acute from chronic renal failure: the osmolar gap is expected to be normal in acute renal failure and elevated in chronic renal failure (4). In reality, the osmolar gap is used infrequently.

PLASMA TONICITY

Because urea passes freely across cell membranes, the effective osmolality or tonicity of the extracellular fluid can be calculated by eliminating urea (BUN) from the plasma osmolality equation.

$$\begin{aligned}\text{Plasma tonicity} &= (2 \times [\text{Na}]) + \frac{[\text{Glucose}]}{18} \\ &= (2 \times 140) + \frac{90}{18} \qquad (40.3) \\ &= 285 \text{ mOsm/kg } H_2O\end{aligned}$$

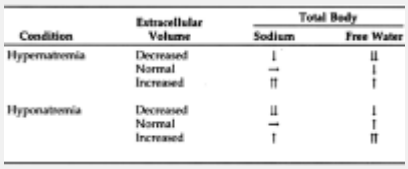
Because the concentration of urea contributes little to the total solute concentration in extracellular fluids, there is little difference between the osmolality and tonicity of the extracellular fluid. This equation

establishes the plasma sodium concentration as the principal determinant of the effective osmolality of extracellular fluid. Because the effective osmolality determines the tendency for water to move into and out of cells, **the plasma sodium concentration is the principal determinant of the relative volumes of the intracellular and extracellular fluids.**

HYPERNATREMIA

The normal plasma (serum) sodium concentration is 135 to 145 mEq/L. Therefore, hypernatremia (i.e., a serum sodium concentration above 145 mEq/L) can be the result of loss of fluid that has a sodium concentration below 135 mEq/L (hypotonic fluid loss) or gain of fluid that has a sodium concentration above 145 mEq/L (hypertonic fluid gain). Each of these

conditions can be identified by assessing the state of the extracellular volume, as shown in Table 40.1.



Condition	Extracellular Volume	Total Body Sodium	Total Body Free Water
Hypernatremia	Decreased	↓	↓↓
	Normal	→	↓
	Increased	↑↑	↑
Hyponatremia	Decreased	↓↓	↓
	Normal	→	↑
	Increased	↑	↑↑

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TABLE 40.1. CHANGES IN TOTAL BODY SODIUM AND WATER IN HYPERNATREMIA AND HYPONATREMIA

EXTRACELLULAR VOLUME

If invasive hemodynamic monitoring is available, the intravascular volume (IVV) can be evaluated by noting the cardiac filling pressures and the cardiac output (as described in Chapter 10, Chapter 11, Chapter 14, and Chapter 16). In the absence of hypoproteinemia (which shifts fluids from the intravascular to extravascular space), the state of the IVV can be used as a reflection of the state of the extracellular volume (ECV).

If invasive hemodynamic monitoring is unavailable, the state of the ECV can be inferred from a few clinical variables. The first is the sudden loss of weight (i.e., in a nonedematous person, a sudden loss of weight over a few days is an indication of a decreased ECV). The second is the presence of peripheral edema (i.e., in the absence of hypoproteinemia, the presence of peripheral edema is an indication of an increased ECV). The third is the concentration of sodium in a random (spot) urine sample (i.e., a urine sodium concentration less than 10 mEq/L is an indication of a decreased ECV). Finally, the clinical

manifestations shown in Table 14.2 can be used as evidence for a decreased ECV.

Once the state of the ECV is determined, the strategies shown in Figure 40.1 can be applied.

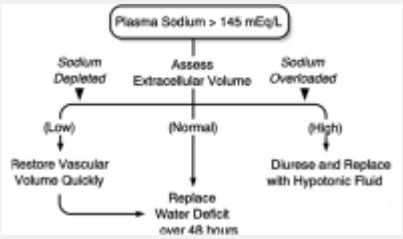

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Figure 40.1. Management strategies for hypernatremia based on the extracellular volume. (From Marino PL, Krasner J, O'Moore P. Fluid and electrolyte expert. Philadelphia: WB Saunders, 1987.)

Low ECV indicates loss of hypotonic fluids. Common causes are excessive diuresis, vomiting, and diarrhea. The management strategy is to replace the sodium deficit quickly (to maintain IVV) and to replace the free water deficit slowly (to prevent intracellular overhydration).

Normal ECV indicates a net loss of free water. This can be seen in diabetes insipidus, or when loss of hypotonic fluids (e.g., diuresis) is treated by replacement with isotonic saline in a 1:1 volume-to-volume ratio. The management strategy is to replace the free water deficit slowly (to prevent intracellular overhydration).

High ECV indicates a gain of hypertonic fluids. This is seen with aggressive use of hypertonic saline or sodium bicarbonate solutions. The management strategy is to induce sodium loss in the urine with diuresis and to replace the urine volume loss with fluids that are hypotonic to the urine.

Each of these conditions is described in more detail in the following sections.

HYPOVOLEMIC HYPERNATREMIA

The most common cause of hypernatremia is loss of hypotonic body fluids. The concentration of sodium in the body fluids that are commonly

lost is shown in Table 40.2. With the exception of small bowel secretions and pancreatic secretions, loss of any of these body fluids will result in hypernatremia.

Fluids Commonly Lost	Sodium Concentration (mEq/L)
Urine*	<10
Diarrhea	40
Gastric secretions	55
Sweat	80
Furosemide diuresis	75
Pancreatic secretions	145
Small bowel secretions	145

* Urinary sodium concentration varies according to daily sodium intake.

View Table

TABLE 40.2. SODIUM CONCENTRATION IN BODY FLUIDS

CONSEQUENCES

All of the body fluids listed in Table 40.2 contain sodium, so the loss of these fluids will be accompanied by deficits in total body sodium as well as TBW. The sodium deficits predispose to hypovolemia, whereas the free water deficits predispose to hypertonicity in the extracellular fluids. Therefore, the two consequences of hypotonic fluid loss are hypovolemia and hypertonicity.

Hypovolemia

The most immediate threat with hypotonic fluid loss is hypovolemia, which predisposes to hypoperfusion of the vital organs. Fortunately, hypovolemia is not as prominent when hypotonic fluids are lost as when whole blood is lost. This is because the resultant hypertonicity draws water out of cells, and this helps maintain the volume of the extracellular (intravascular) fluid compartment.

Hypertonicity

The hypertonicity of the extracellular fluids predisposes to cellular dehydration. The most serious consequence of hypertonic hypernatremia is a metabolic encephalopathy (6). Clinical findings include depressed consciousness that can progress to frank coma, generalized seizures, and focal neurologic deficits. Hypernatremic encephalopathy has an associated mortality of up to 50% (6), but management should proceed slowly.

VOLUME REPLACEMENT

The most immediate concern in hypovolemic hypernatremia is to replace volume deficits and to maintain the cardiac output. Volume

replacement can be guided by the cardiac filling pressures and the cardiac output, or by the clinical variables shown in Table 14.2. When solute losses are severe and hemodynamic compromise is present, colloid fluid replacement with 5% albumin or 6% hetastarch can rapidly restore the IVV, as described in Chapter 15. When crystalloid fluids are given for volume replacement, isotonic saline should always be used and less concentrated fluids (e.g., half-normal saline), which predispose to cellular overhydration, should be avoided.

FREE WATER REPLACEMENT

When hypovolemia has been corrected, the next step is to calculate and replace the free water deficit. The calculation of free water deficit is based on the assumption that the product of TBW and plasma sodium concentration (P_{Na}) is always constant.

$$\text{Current TBW} \times \text{Current } P_{Na} = \text{Normal TBW} \times \text{Normal } P_{Na} \qquad (40.4)$$

Using a normal plasma sodium concentration of 140 mEq/L and rearranging terms yields the following relationship:

$$\text{Current TBW} = \text{Normal TBW} \times (140/\text{Current } P_{Na}) \qquad (40.5)$$

The normal TBW (in liters) usually is 60% of lean body weight (in kg) in men and 50% of lean body weight in women. However, in hypernatremia associated with free water deficits, the normal TBW should be approximately 10% less than usual (3). Thus in men, the normal TBW is 0.5 × body weight (kg), and in women, the normal TBW is 0.4 × body weight (in kg). Once the current TBW is calculated, the water deficit is taken as the difference between the normal TBW and the current TBW.

$$\text{TBW deficit (L)} = \text{Normal TBW} - \text{Current TBW} \qquad (40.6)$$

Example Calculation

Assume that an adult man with a lean body weight of 70 kg has a plasma sodium of 160 mEq/L. The normal TBW will be 0.5 × 70 = 35 L. The current TBW will be 35 × 140/160 = 30.5 L. The TBW deficit will be 35 – 30.5 = 4.5 L.

Replacement Volume

The volume of the replacement fluid needed to correct the water deficit is determined by the concentration of sodium in the replacement fluid. The replacement volume can be determined as follows (1):

$$\text{Replacement volume (L)} = \text{TBW deficit} \times (1/1 - X) \qquad (40.7)$$

where X is the ratio of the sodium concentration in the replacement fluid to the sodium concentration in isotonic saline (X = replacement fluid Na/154). If the

water deficit is 4.5 L and the replacement fluid is half-normal saline (Na = 75 mEq/L), the replacement volume will be 4.5 × (1/0.5) = 9 L.

Cerebral Edema

The brain cells initially shrink in response to a hypertonic extracellular fluid, but cell volume is restored within hours. This restoration of cell volume is attributed to the generation of osmotically active substances called idiogenetic osmoles (6). Once the brain cell volume is restored to normal, the aggressive replacement of free water can predispose to cerebral edema. To limit the risk of cerebral edema, **free water deficits should be replaced slowly, over 48 to 72 hours** (6).

DIABETES INSIPIDUS

The most noted cause for hypernatremia without apparent volume deficits is diabetes insipidus (DI), which is a condition of impaired renal water conservation (7). This condition results in excessive loss of urine that is almost pure water (devoid of solute). The underlying problem in DI is related to antidiuretic hormone (ADH), a hormone secreted by the posterior pituitary gland that promotes water reabsorption in the distal tubule. Two defects related to ADH can occur in DI:

Central DI is caused by inhibition of ADH release from the posterior pituitary. Common causes of central DI in critically ill patients include closed head injury, anoxic encephalopathy, and meningitis (5,7). The onset is heralded by polyuria that usually is evident within 24 hours of the inciting event.

Nephrogenic DI is caused by defective end-organ responsiveness to ADH. Possible causes of nephrogenic DI in critically ill patients includes hypokalemia, aminoglycosides, amphotericin, radiocontrast dyes, and the polyuric phase of ATN. The defect in urine concentrating ability in nephrogenic DI is not as severe as it is in central DI.

DIAGNOSIS

The hallmark of DI is a dilute urine in the face of plasma hypertonicity. In central DI, the urine osmolarity is often below 200 mOsm/L, whereas in nephrogenic DI, the urine osmolarity is usually between 200 and 500 mOsm/L (5). The diagnosis of DI is confirmed by noting the urinary response to fluid restriction. Failure of the urine osmolarity to increase more than 30 mOsm/L in the first hours of complete fluid restriction is diagnostic of DI. The fluid losses can be excessive during fluid restriction in DI (particularly central DI), and thus fluid restriction must be monitored carefully. Once the diagnosis of DI is confirmed,

the response to vasopressin (5 units intravenously) will differentiate central from nephrogenic DI. In central DI, the urine osmolality increases by at least 50% almost immediately after vasopressin administration, whereas the urine osmolality remains unchanged after vasopressin in nephrogenic DI.

MANAGEMENT

The fluid loss in DI is almost pure water, so the replacement strategy is aimed at replacing free water deficits only. The water deficit is calculated as described previously, and the free water deficit is corrected slowly (over 2 to 3 days) to limit the risk of cerebral edema. In central DI, vasopressin administration is also required to prevent ongoing free water losses. The usual dose is 5 to 10 units of aqueous vasopressin subcutaneously every 6 to 8 hours (5,7). The serum sodium must be monitored carefully during vasopressin therapy because water intoxication and hyponatremia can occur if the central DI begins to resolve.

HYPERVOLEMIC HYPERNATREMIA

Hypernatremia from hypertonic fluid gain is uncommon. Possible causes are hypertonic saline resuscitation, sodium bicarbonate infusions for metabolic acidosis (see Table 37.1), and ingestion of excessive amounts of table salt (8).

MANAGEMENT

In patients with normal renal function, excess sodium and water are excreted rapidly. When renal sodium excretion is impaired, it might be necessary to increase renal sodium excretion with a diuretic (e.g., furosemide). Because the sodium concentration in urine during furosemide diuresis is approximately 75 mEq/L, excessive urine output will aggravate the hypernatremia (because the urine is hypotonic to plasma). Therefore, urine volume losses must be partially replaced with a fluid that is hypotonic to the urine.

HYPERGLYCEMIA

The formula for plasma tonicity presented earlier predicts that hyperglycemia will be accompanied by a hypertonic extracellular fluid. When progressive hyperglycemia does not result in ketosis, the major clinical consequence is a hypertonic encephalopathy similar to the one described for hypernatremia (6). The syndrome of **nonketotic hyperglycemia** (NKH) usually is seen in patients who have enough endogenous insulin to prevent ketosis. The condition usually is precipitated by a physiological stress (e.g., infection, trauma), and the patients may or may not have a prior history of diabetes mellitus (9). The plasma

glucose is often 1000 mg/dL or higher (9) (whereas in ketoacidosis, the plasma glucose is usually below 800 mg/dL). The persistent loss of glucose in the urine produces an osmotic diuresis that can lead to profound volume losses.

CLINICAL MANIFESTATIONS

Patients with NKH usually have an altered mental status and may show signs of hypovolemia. The altered mental status can progress to frank coma when the plasma tonicity rises above 330 mOsm/kg H_2O (9). Advanced cases of encephalopathy can be accompanied by generalized seizures and focal neurologic deficits, as described for hypernatremic encephalopathy.

MANAGEMENT

The fluid management of NKH is similar to that described for hypovolemic hypernatremia. Volume deficits tend to be more profound in NKH than in simple hypovolemic hypernatremia because of the osmotic diuresis that accompanies the glycosuria. Therefore, rapid correction of the IVV (i.e., with 5% albumin or isotonic saline) may be necessary.

Free Water Deficit

Once the IVV is restored, free water deficits are estimated and replaced slowly. However when calculating the free water deficit that accompanies hyperglycemia, it is necessary to correct the plasma sodium for the increase in plasma glucose. This is because the hyperglycemia draws water from the intracellular space, and this creates a dilutional effect on the plasma sodium concentration. The decrease in plasma sodium in hypernatremia can vary according to the state of the ECV. In general, **for every 100 mg/dL increment in the plasma glucose, the plasma sodium should fall by 1.6 to 2 mEq/L** (10). Therefore, for a patient with a plasma glucose of 1000 mg/dL and a measured plasma sodium of 145 mEq/L, the actual or corrected plasma sodium will average 145 + (900/100 × 1.8) = 161 mEq/L (the factor 1.8 is taken as the average value between 1.6 and 2 mEq/L).

The restoration of brain cell volume can occur rapidly in hypertonic states due to hyperglycemia (9). Therefore, the free water replacement should be particularly judicious in NKH.

Insulin Therapy

Because insulin drives both glucose and water into cells, insulin therapy can aggravate hypovolemia. Therefore, in patients who are hypovolemic, insulin should be withheld until the IVV is restored. Once this is accomplished, insulin therapy can be given as advised for

diabetic ketoacidosis (see Table 37.2). The insulin requirement will diminish as the hypertonic condition is corrected, so plasma glucose concentrations should be monitored hourly during intravenous insulin therapy in NKH.

HYPONATREMIA

Hyponatremia (serum sodium less than 135 mEq/L) is found in up to 4.5% of hospitalized elderly patients (11) and in 1% of postoperative patients (12). It is particularly prevalent in patients with the acquired immunodeficiency syndrome (AIDS) and can be seen in up to 40% of hospitalized patients with AIDS (13). The mortality in hyponatremic patients is as much as double the mortality in patients with a normal plasma sodium concentration (11,13). This increase in mortality can be a reflection of the treatment as well as the consequences of hyponatremia.

PSEUDOHYPONATREMIA

Extreme elevations in plasma lipids or proteins increase the plasma volume and can reduce the measured plasma sodium concentration. The increase in plasma volume in these situations is in the nonaqueous phase of plasma, and because the sodium is contained in the aqueous phase of plasma, the hyponatremia in this situation does not represent a decrease in extracellular sodium relative to extracellular water (i.e., true or hypotonic hyponatremia). This condition is therefore called *pseudohyponatremia.* Because the nonaqueous phase of plasma represents only 7% of the total plasma volume, large increases in plasma lipids and plasma proteins are needed to produce significant decreases in the measured plasma sodium concentration. The correction factors for hyperlipidemia and hyperproteinemia are as follows (1):

- Plasma triglycerides (g/L) × 0.002 = mEq/L decrease in plasma Na.
- Plasma protein level minus 8 (g/dL) × 0.025 = mEq/L decrease in plasma Na.

Ion-Specific Electrodes

The conventional method for measuring plasma sodium (flame emission spectrophotometry) includes both the aqueous and nonaqueous phases of plasma. However, the newer ion-specific sodium electrodes measure the sodium concentration only in the aqueous phase of plasma. Therefore, pseudohyponatremia will not occur when ion-specific electrodes are used to measure the plasma sodium concentration (14).

HYPOTONIC HYPONATREMIA

True or hypotonic hyponatremia represents an increase in free water relative to sodium in the extracellular fluids. It does *not* necessarily represent an increase in the volume of extracellular fluids. As shown in Table 40.1, the ECV can be low, normal, or high in patients with hyponatremia. The diagnostic approach to hyponatremia can begin with an assessment of the ECV, as shown in Figure 40.2 (14,15). (The assessment of ECV is described earlier, for the assessment of hypernatremia.)

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Figure 40.2. Diagnostic approach to hyponatremia. *SIADH* = syndrome of inappropriate antidiuretic hormone.

HYPOVOLEMIC HYPONATREMIA

This condition is characterized by fluid losses combined with volume replacement using a fluid that is hypotonic to the lost fluid (e.g., diuresis replaced by drinking tap water). The result is a net loss of sodium relative to free water, which decreases both the ECV and the extracellular sodium concentration. The concentration of sodium in a random (spot) urine sample can sometimes help determine if the sodium loss is renal or extrarenal in origin.

Site of Sodium Loss	Urine Sodium
Renal	>20 mEq/L
Extrarenal	<10 mEq/L

Renal sodium losses would be seen in diuretic overuse and in adrenal

insufficiency, whereas extrarenal sodium losses can occur with diarrhea and persistent vomiting.

ISOVOLEMIC HYPONATREMIA

Isovolemic hyponatremia is characterized by a small gain in free water, but not enough to be clinically detected (approximately 5 L of excess water is necessary to produce detectable peripheral edema in the average-size adult). In this situation, the major disorders to consider are inappropriate (nonosmotic) release of ADH and acute water intoxication (psychogenic polydipsia). The urine sodium and urine osmolality will help distinguish between these two disorders.

Clinical Disorder	Urine Sodium	Urine Osmolality
Inappropriate ADH	>20 mEq/L	>100 mOsm/kg H_2O
Water intoxication	<10 mEq/L	<100 mOsm/kg H_2O

The inappropriate (nonosmotic) release of ADH is characterized by an inappropriately concentrated urine (urine osmolality above 100 mOsm/kg H_2O) in the face of a hypotonic plasma (plasma tonicity below 290 mOsm/kg H_2O). This condition can be seen in certain groups of “stressed” patients, such as patients who have undergone recent surgery. It can also be produced by a variety of tumors and infections. This latter condition is known as the *syndrome of inappropriate ADH* (SIADH), and it can be accompanied by severe hyponatremia (plasma sodium below 120 mEq/L).

HYPERVOLEMIC HYPONATREMIA

Hypervolemic hyponatremia represents an excess of sodium and water, with the water gain exceeding the sodium gain. In this situation, the urine sodium can sometimes help identify the source of the problem.

Common Causes	Urine Sodium
Heart failure	<20 mEq/L
Renal failure	>20 mEq/L
Hepatic failure	<20 mEq/L

The urine sodium can be misleading if the patient is also receiving diuretics (which are commonly used in these conditions). The clinical picture is usually helpful, although these conditions can co-exist in critically ill patients.

SYMPTOMATIC HYPONATREMIA

The major complication of hyponatremia is a metabolic encephalopathy, which can be both irreversible and fatal (12,16,17). This condition is due to cerebral edema and increased intracranial pressure (17). In

addition to having the same manifestations as the encephalopathy associated with the hypertonic syndromes (i.e., depressed level of consciousness, seizures, and focal neurologic findings), this encephalopathy can be accompanied by the acute respiratory distress syndrome (18).

In addition to hyponatremic encephalopathy another distinct encephalopathy is associated with the therapy of hyponatremia, particularly when the hyponatremia is corrected too rapidly (17). This encephalopathy is characterized by diffuse demyelinating lesions and can be accompanied by pituitary damage and oculomotor nerve palsies. A specific type of demyelinating disorder known as central pontine myelinolysis has also been attributed to rapid correction of hyponatremia (19). As described in the following section, the risk of this second encephalopathy has led to specific recommendations for limiting the maximum rate and end-point of corrective therapy.

MANAGEMENT STRATEGIES

The management of hyponatremia is determined by the state of the ECV (i.e., low, normal, or high) and by the presence or absence of neurologic symptoms. Symptomatic hyponatremia requires more aggressive corrective therapy than asymptomatic hyponatremia. However, to limit the risk of a demyelinating encephalopathy, **the rate of rise in plasma sodium should not exceed 0.5 mEq/L/hour and the final plasma sodium concentration should not exceed 130 mEq/L** (17). The general management strategies based on the ECV are as follows:

Low ECV:

Infuse hypertonic saline (3% NaCl) in symptomatic patients, and isotonic saline in asymptomatic patients.

Normal ECV:

Combine furosemide diuresis with infusion of hypertonic saline in symptomatic patients, or isotonic saline in asymptomatic patients.

High ECV:

Use furosemide-induced diuresis in asymptomatic patients. In symptomatic patients, combine furosemide diuresis with judicious use of hypertonic saline.

SODIUM REPLACEMENT

When corrective therapy requires the infusion of isotonic saline or hypertonic saline, the replacement therapy can be guided by the calculated sodium deficit. This is determined as follows (using a plasma sodium of 130 mEq/L as the desired end-point of replacement therapy):

$$\text{Sodium deficit (mEq)} = \text{Normal TBW} \times (130 - \text{Current } P_{Na}) \quad (40.8)$$

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The normal TBW (in liters) is 60% of the lean body weight (in kg) in men, and 50% of the lean body weight in women. Thus, for a 60 kg woman with a plasma sodium of 120 mEq/L, the sodium deficit will be 0.5 × 60 × (130 – 120) = 300 mEq.

Because 3% sodium chloride contains 513 mEq of sodium per liter, the volume of hypertonic saline needed to correct a sodium deficit of 300 mEq will be 300/513 = 585 mL. Using a maximum rate of rise of 0.5 mEq/L/hour for the plasma sodium (to limit the risk of a demyelinating encephalopathy), the sodium concentration deficit of 10 mEq/L in the previous example should be corrected over at least 20 hours. Thus, the maximum rate of hypertonic fluid administration will be 585/20 = 29 mL/hour. If isotonic saline is used for sodium replacement, the replacement volume will be 3.3 times the replacement volume of the hypertonic 3% saline solution.

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