Review Articles

Primary Care

HYPERNATREMIA

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THE serum sodium concentration and thus serum osmolality are closely controlled by water homeostasis, which is mediated by thirst, arginine vasopressin, and the kidneys.[1] A disruption in the water balance is manifested as an abnormality in the serum sodium concentration — hypernatremia or hyponatremia.[2,3] Hypernatremia, defined as a rise in the serum sodium concentration to a value exceeding 145 mmol per liter, is a common electrolyte disorder. Because sodium is a functionally impermeable solute, it contributes to tonicity and induces the movement of water across cell membranes.[4] Therefore, hypernatremia invariably denotes hypertonic hyperosmolality and always causes cellular dehydration, at least transiently (Fig. 1). The resultant morbidity may be inconsequential, serious, or even life-threatening.[5] Hypernatremia frequently develops in hospitalized patients as an iatrogenic condition, and some of its most serious complications result not from the disorder itself but from inappropriate treatment of it.[6,7] In this article, we focus on the management of hypernatremia, emphasizing a quantitative approach to the correction of the fluid imbalance.[8]

CAUSES

Hypernatremia represents a deficit of water in relation to the body's sodium stores, which can result from a net water loss or a hypertonic sodium gain (Table 1). Net water loss accounts for the majority of cases of hypernatremia.[9-11] It can occur in the absence of a sodium deficit (pure water loss) (Fig. 1B) or in its presence (hypotonic fluid loss) (Fig. 1C and 1D). Hypertonic sodium gain usually results from clinical interventions or accidental sodium loading (Table 1 and Fig. 1E).

Because sustained hypernatremia can occur only when thirst or access to water is impaired, the groups at highest risk are patients with altered mental status, intubated patients, infants, and elderly persons.[12] Hypernatremia in infants usually results from diarrhea, whereas in elderly persons it is usually associated with infirmity or febrile illness.[6,13,14] Thirst impairment also occurs in elderly patients.[15,16] Frail nursing home residents and hospitalized patients are prone to hypernatremia because they depend on others for their water requirements.[7]

CLINICAL MANIFESTATIONS

Signs and symptoms of hypernatremia largely reflect central nervous system dysfunction and are prominent when the increase in the serum sodium concentration is large or occurs rapidly (i.e., over a period of hours).[1,6] Most outpatients with hypernatremia are either very young or very old.[17] Common symptoms in infants include hyperpnea, muscle weakness, restlessness, a characteristic high-pitched cry, insomnia, lethargy, and even coma.[5,13] Convulsions are typically absent except in cases of inadvertent sodium loading or aggressive rehydration.[14,18,19] Unlike infants, elderly patients generally have few symptoms until the serum sodium concentration exceeds 160 mmol per liter.[17,20] Intense thirst may be present initially, but it dissipates as the disorder progresses and is absent in patients with hypodipsia.[5] The level of consciousness is correlated with the severity of the hypernatremia.[6] Muscle weakness, confusion, and coma are sometimes manifestations of coexisting disorders rather than of the hypernatremia itself.

Unlike hypernatremia in outpatients, hospital-acquired hypernatremia affects patients of all ages.[7] The clinical manifestations are even more elusive in hospitalized patients because they often have preexisting neurologic dysfunction. As in children, rapid sodium loading in adults can cause convulsions and coma.[5,21] In patients of all ages, orthostatic hypotension and tachycardia reflect marked hypovolemia.

Brain shrinkage induced by hypernatremia can cause vascular rupture, with cerebral bleeding, subarachnoid hemorrhage, and permanent neurologic damage or death. Brain shrinkage is countered by an adaptive response that is initiated promptly and consists of solute gain by the brain that tends to restore lost water. This response leads to the normalization of brain volume and accounts for the milder symptoms of hypernatremia that develops slowly (Fig. 2).[22-24] However, the normalization of brain volume does

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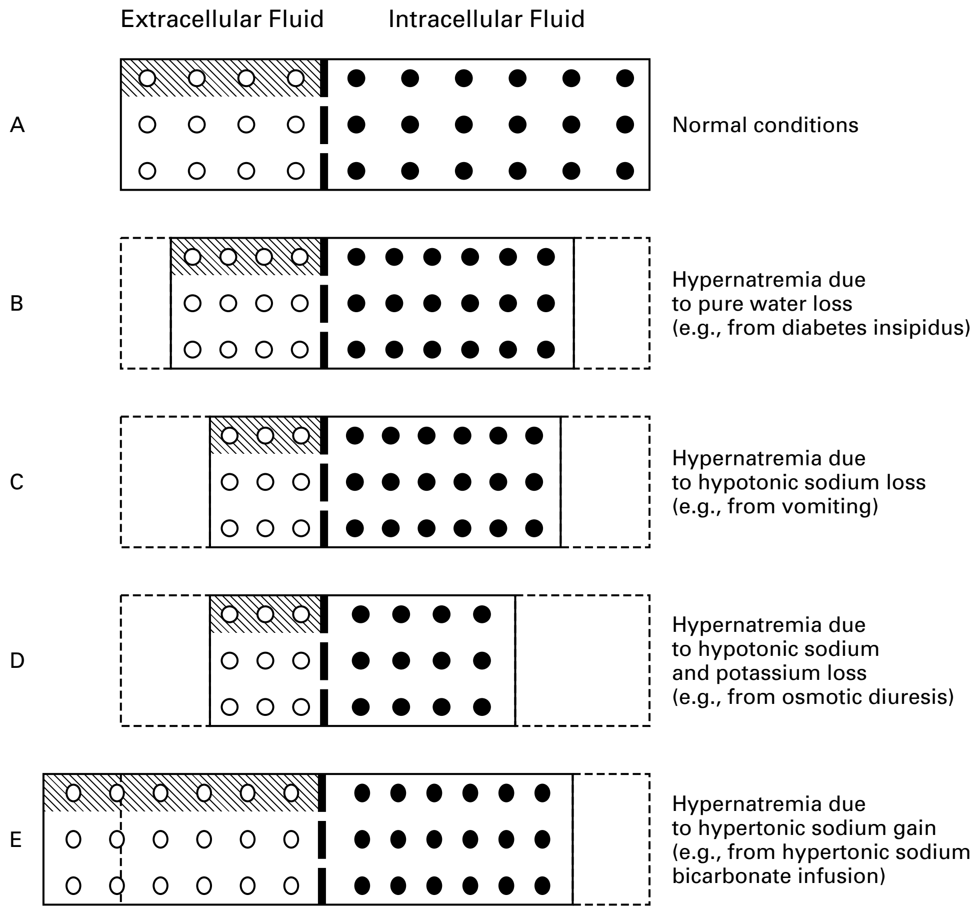

Figure 1. Extracellular-Fluid and Intracellular-Fluid Compartments under Normal Conditions and during States of Hypernatremia.

Normally, the extracellular-fluid and intracellular-fluid compartments account for 40 and 60 percent of total body water, respectively (Panel A). Pure water loss reduces the size of each compartment proportionately (Panel B). Contrary to common belief, the volume of extracellular fluid in this setting is reduced, not normal, although the reduction is often not clinically evident. The sodium content of extracellular fluid remains unaltered, yet 1 of each 2.5 liters of water that is lost is from the extracellular-fluid compartment. Hypotonic sodium loss causes a relatively larger loss of volume in the extracellular-fluid compartment than in the intracellular-fluid compartment (Panel C). Potassium loss in addition to hypotonic sodium loss further reduces the intracellular-fluid compartment (Panel D). Hypertonic sodium gain results in an increase in extracellular fluid but a decrease in intracellular fluid (Panel E). In each panel, the open circles denote sodium, and the solid circles potassium; the broken line between the two compartments represents the cell membrane, and the shading indicates the intravascular volume.

not correct hyperosmolality in the brain. In patients with prolonged hyperosmolality, aggressive treatment with hypotonic fluids may cause cerebral edema, which can lead to coma, convulsions, and death (Fig. 2).[14,18,19]

The mortality rate associated with hypernatremia varies widely according to the severity of the condition and the rapidity of its onset. It is difficult, however, to separate the contribution of hypernatremia to mortality from the contribution of underlying illnesses.[11,23]

MANAGEMENT

Proper treatment of hypernatremia requires a two-pronged approach: addressing the underlying cause and correcting the prevailing hypertonicity.[3,11] Managing the underlying cause may mean stopping gastrointestinal fluid losses; controlling pyrexia, hyperglycemia, and glucosuria; withholding lactulose and diuretics; treating hypercalcemia and hypokalemia; moderating lithium-induced polyuria; or correcting the feeding preparation. In patients with hypernatremia that has developed over a period of hours (e.g., those with accidental sodium loading) rapid correction improves the prognosis without increasing the risk of cerebral edema, because accumulated electrolytes are rapidly extruded from brain cells.[11,22] In such patients, reducing the serum sodium concentration by 1 mmol per liter per hour is appropriate.[11] A slow-

TABLE 1. CAUSES OF HYPERNATREMIA.

- **Net water loss**
- Pure water
  - Unreplaced insensible losses (dermal and respiratory)
  - Hypodipsia
  - Neurogenic diabetes insipidus
    - Post-traumatic
    - Caused by tumors, cysts, histiocytosis, tuberculosis, sarcoidosis
    - Idiopathic
    - Caused by aneurysms, meningitis, encephalitis, Guillain–Barré syndrome
    - Caused by ethanol ingestion (transient)
  - Congenital nephrogenic diabetes insipidus
  - Acquired nephrogenic diabetes insipidus
    - Caused by renal disease (e.g., medullary cystic disease)
    - Caused by hypercalcemia or hypokalemia
    - Caused by drugs (lithium, demeclocycline, foscarnet, methoxyflurane, amphotericin B, vasopressin V_2–receptor antagonists)
- Hypotonic fluid
  - Renal causes
    - Loop diuretics
    - Osmotic diuresis (glucose, urea, mannitol)
    - Postobstructive diuresis
    - Polyuric phase of acute tubular necrosis
    - Intrinsic renal disease
  - Gastrointestinal causes
    - Vomiting
    - Nasogastric drainage
    - Enterocutaneous fistula
    - Diarrhea
    - Use of osmotic cathartic agents (e.g., lactulose)
  - Cutaneous causes
    - Burns
    - Excessive sweating
- **Hypertonic sodium gain**
- Hypertonic sodium bicarbonate infusion
- Hypertonic feeding preparation
- Ingestion of sodium chloride
- Ingestion of sea water
- Sodium chloride–rich emetics
- Hypertonic saline enemas
- Intrauterine injection of hypertonic saline
- Hypertonic sodium chloride infusion
- Hypertonic dialysis
- Primary hyperaldosteronism
- Cushing's syndrome

er pace of correction is prudent in patients with hypernatremia of longer or unknown duration, because the full dissipation of accumulated brain solutes occurs over a period of several days (Fig. 2).[19,22] In such patients, reducing the serum sodium concentration at a maximal rate of 0.5 mmol per liter per hour prevents cerebral edema and convulsions.[25,26] Consequently, we recommend a targeted fall in the serum sodium concentration of 10 mmol per liter per day for all patients with hypernatremia except those in whom the disorder has developed over a period of hours. The goal of treatment is to reduce the serum sodium concentration to 145 mmol per liter. Since ongoing losses of hypotonic fluids, whether obligatory or incidental, will aggravate the hypernatremia, allowance for these losses must also be made. In addition, patients with seizures require prompt anticonvulsant therapy and adequate ventilation.

The preferred route for administering fluids is the oral route or a feeding tube; if neither is feasible, fluids should be given intravenously. Only hypotonic fluids are appropriate, including pure water, 5 percent dextrose, 0.2 percent sodium chloride (referred to as one-quarter isotonic saline), and 0.45 percent sodium chloride (one-half isotonic saline). The more hypotonic the infusate, the lower the infusion rate required. Because the risk of cerebral edema increases with the volume of the infusate, the volume should be restricted to that required to correct hypertonicity.[25] Except in cases of frank circulatory compromise, 0.9 percent sodium chloride (isotonic saline) is unsuitable for managing hypernatremia.

After selecting the appropriate infusate, the physician must determine the rate of infusion. This can be easily calculated with the use of a formula (formula 1 in Table 2) that estimates the change in the serum sodium concentration caused by the retention of 1 liter of any infusate.[8] The required volume of infusate, and hence the infusion rate, is determined by dividing the change in the serum sodium concentration targeted for a given treatment period by the value obtained from formula 1. Table 2 also shows the sodium concentrations of commonly used infusates, their fractional distribution in the extracellular fluid, and clinical estimates of total body water.[27] The cases described below illustrate the various forms of hypernatremia and their management.

Pure Water Loss

A 76-year-old man presents with a severe obtundation, dry mucous membranes, decreased skin turgor, fever, tachypnea, and a blood pressure of 142/82 mm Hg without orthostatic changes. The serum sodium concentration is 168 mmol per liter, and the body weight is 68 kg. Hypernatremia caused by pure water depletion due to insensible losses is diagnosed (Fig. 1B), and an infusion of 5 percent dextrose is planned. The estimated volume of total body water is 34 liters (0.5×68). According to formula 1, the retention of 1 liter of 5 percent dextrose will reduce the serum sodium concentration by 4.8 mmol per liter ($[0-168]\div[34+1]=-4.8$). The goal of treatment is to reduce the serum sodium concentration by approximately 10 mmol per liter over a period of 24 hours. Therefore, 2.1 liters of the solution ($10\div 4.8$) is required. With 1.5 liters added to compensate for average obligatory water losses over the 24-hour period, a total of 3.6 liters will be administered for the next 24 hours, or 150 ml per hour. The serum glucose concentration will be monitored, with insulin therapy started at the first indication of hyperglycemia, a complication that would aggravate the hypertonicity. Close monitoring of the patient's clinical status and laboratory values, initially at intervals of

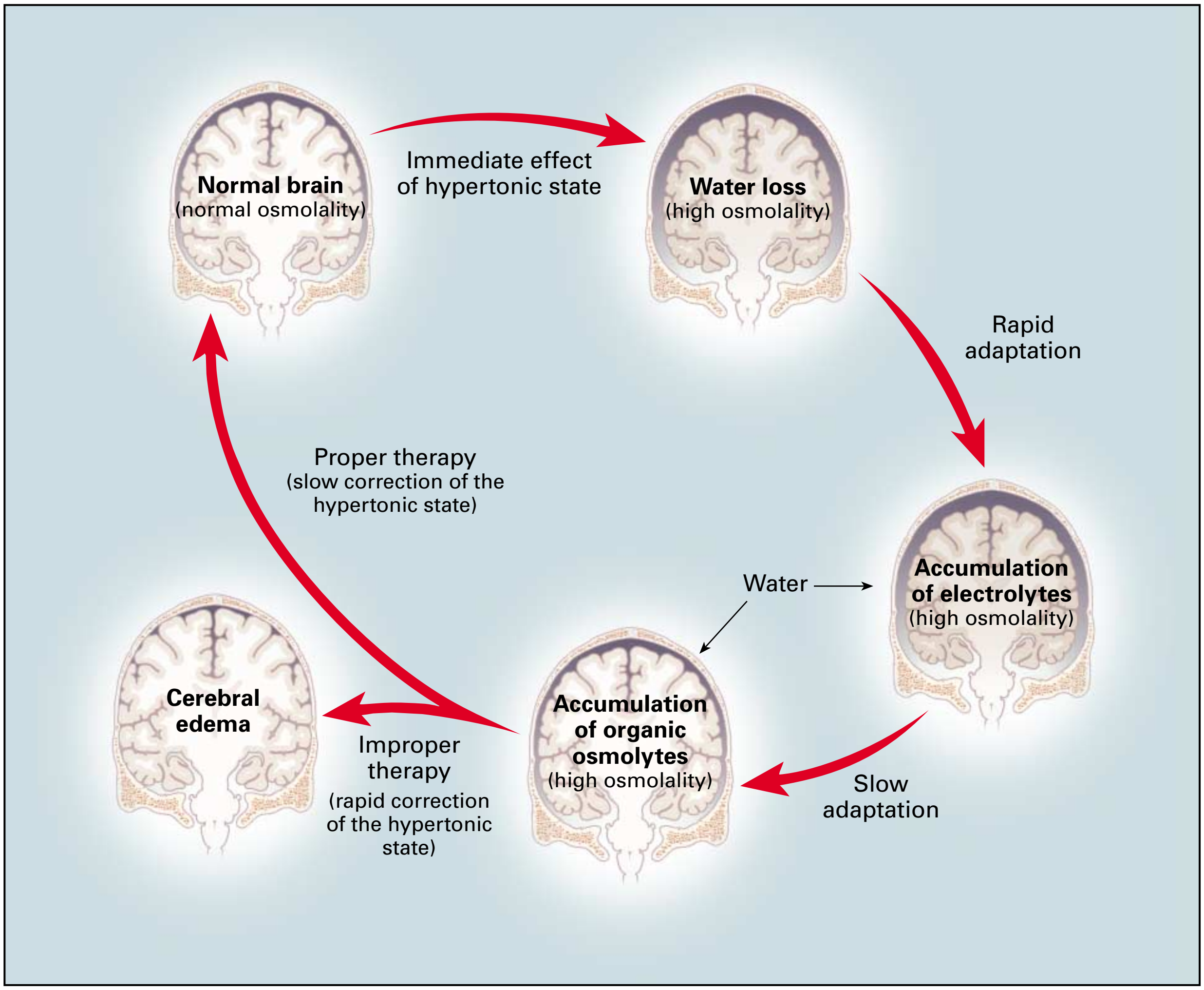

Figure 2. Effects of Hypernatremia on the Brain and Adaptive Responses.

Within minutes after the development of hypertonicity, loss of water from brain cells causes shrinkage of the brain and an increase in osmolality. Partial restitution of brain volume occurs within a few hours as electrolytes enter the brain cells (rapid adaptation). The normalization of brain volume is completed within several days as a result of the intracellular accumulation of organic osmolytes (slow adaptation). The high osmolality persists despite the normalization of brain volume. Slow correction of the hypertonic state reestablishes normal brain osmolality without inducing cerebral edema, as the dissipation of accumulated electrolytes and organic osmolytes keeps pace with water repletion. In contrast, rapid correction may result in cerebral edema as water uptake by brain cells outpaces the dissipation of accumulated electrolytes and organic osmolytes. Such overly aggressive therapy carries the risk of serious neurologic impairment due to cerebral edema.

six to eight hours, will guide adjustments in the administration of fluids.

Hypotonic Sodium Loss

A 58-year-old woman with postoperative ileus is undergoing nasogastric suction. She is obtunded and has diminished skin turgor and mild orthostatic hypotension. The serum sodium concentration is 158 mmol per liter, the potassium concentration is 4.0 mmol per liter, and the body weight is 63 kg. Hypernatremia caused by hypotonic fluid loss is diagnosed (Fig. 1C), and an infusion of 0.45 percent sodium chloride is planned, with the goal of decreasing the serum sodium concentration by 5 mmol per liter over the next 12 hours. Although there is evidence of a depletion in the volume of extracellular fluid, the patient's hemodynamic status is not sufficiently compromised to warrant the initial use of 0.9 percent sodium chloride. The estimated volume of total body water is 31.5 liters (0.5×63). It is estimated that the retention of 1 liter of 0.45 percent sodium chloride will reduce the serum sodium concentration

TABLE 2. FORMULAS FOR USE IN MANAGING HYPERNATREMIA AND CHARACTERISTICS OF INFUSATES.

FORMULA*	CLINICAL USE
1. Change in serum $Na^+ = \dfrac{\text{infusate } Na^+ - \text{serum } Na^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate on serum Na^+
2. Change in serum $Na^+ = \dfrac{(\text{infusate } Na^+ + \text{infusate } K^+) - \text{serum } Na^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate containing Na^+ and K^+ on serum Na^+

INFUSATE	INFUSATE Na^+	EXTRACELLULAR-FLUID DISTRIBUTION
	mmol per liter	%
5% Dextrose in water	0	40
0.2% Sodium chloride in 5% dextrose in water	34	55
0.45% Sodium chloride in water	77	73
Ringer's lactate	130	97
0.9% Sodium chloride in water	154	100

*The numerator in formula 1 is a simplification of the expression (infusate $Na^+ -$ serum Na^+) $\times$ 1 liter, with the value yielded by the equation in millimoles per liter.[8] The estimated total body water (in liters) is calculated as a fraction of body weight. The fraction is 0.6 in children; 0.6 and 0.5 in nonelderly men and women, respectively; and 0.5 and 0.45 in elderly men and women, respectively.[27] Normally, extracellular and intracellular fluids account for 40 and 60 percent of total body water, respectively.[27]

by 2.5 mmol per liter ($[77-158] \div [31.5+1] = -2.5$). Since the goal is to reduce the serum sodium concentration by 5 mmol per liter over the next 12 hours, 2 liters of the solution is required ($5 \div 2.5$). With 1 liter added to compensate for ongoing losses of gastric and other fluids, a total of 3 liters will be administered for the next 12 hours, or 250 ml per hour.

After 12 hours, the patient's serum sodium concentration is 155 mmol per liter. She is febrile and mildly somnolent but hemodynamically stable. Her weight is 64 kg, and the estimated volume of total body water is 32 liters (0.5×64). The physician is dissatisfied with the pace of correction and decides to switch to 0.2 percent sodium chloride, with the goal of reducing the serum sodium concentration by 10 mmol per liter over the next 24 hours. The retention of 1 liter of this solution is estimated to reduce the serum sodium concentration by 3.7 mmol per liter ($[34-155] \div [32+1] = -3.7$). Thus 2.7 liters of solution is required ($10 \div 3.7$). With the addition of 2 liters to compensate for ongoing water and electrolyte losses, a total of 4.7 liters will be administered for the next 24 hours, or approximately 200 ml per hour.

Hypotonic Sodium and Potassium Loss

A 62-year-old man with advanced alcoholic cirrhosis is receiving lactulose for the management of hepatic encephalopathy. On examination, confusion, ascites, and asterixis are present. The blood pressure is 105/58 mm Hg while the patient is in the supine position, and the pulse is 110 beats per minute. The serum sodium concentration is 160 mmol per liter, the potassium concentration is 2.6 mmol per liter, and the body weight is 64 kg. The hypernatremia reflects hypotonic sodium and potassium losses induced by lactulose therapy (Fig. 1D). Thus, in addition to the withdrawal of lactulose, 0.2 percent sodium chloride containing 20 mmol of potassium chloride per liter will be administered. With the presence of ascites, the estimated volume of total body water is about 38 liters (0.6×64). Because the serum sodium concentration is determined by the ratio of the "exchangeable" (i.e., osmotically active) portions of the body's sodium and potassium content to the total volume of body water,[28] the addition of potassium to the infusate requires its inclusion in the calculation of the change in the serum sodium concentration. Formula 2, a simple derivative of formula 1 (Table 2), takes into account the potassium concentration of the infusate. According to this formula, the retention of 1 liter of 0.2 percent sodium chloride containing 20 mmol of potassium chloride will reduce the serum sodium concentration by 2.7 mmol per liter ($[(34+20)-160] \div [38+1] = -2.7$). To reduce the serum sodium concentration by 10 mmol per liter over the next 24 hours, 3.7 liters of solution ($10 \div 2.7$) is required. With 1.5 liters added to compensate for ongoing obligatory fluid and electrolyte losses, a total of 5.2 liters will be administered over the next 24 hours, or about 220 ml per hour.

Clearly, the use of formula 1 (and its derivative, formula 2) permits a quantitative and flexible approach to the prescription of fluids that can easily accommodate different infusates and treatment periods. We do not recommend using the conventional formula:

$$\text{water deficit} = \text{total body water} \times (1 - [140 \div \text{serum sodium concentration}]).$$

Although this formula provides an adequate estimate of the water deficit in patients with hypernatremia caused by pure water loss, it underestimates the deficit in patients with hypotonic fluid loss (Fig. 1). Furthermore, the conventional formula is not useful when sodium and potassium, in addition to water, must be prescribed.[8]

Hypertonic Sodium Gain

A 60-year-old man has received 10 ampules of sodium bicarbonate over a period of six hours during resuscitation after recurrent cardiac arrest. He is stuporous and is undergoing mechanical ventilation. His blood pressure is 138/86 mm Hg, and peripheral edema (+++) is present. The serum sodium concentration is 156 mmol per liter, the body weight is 85 kg, and the urinary output is 30 ml per hour. The hypernatremia is caused by hypertonic sodium gain (Fig. 1E), and its correction requires that the excess sodium and water be excreted. The administration of furosemide alone will not suffice, because furosemide-induced diuresis is equivalent to one-half isotonic saline solution; thus, the hypernatremia will be aggravated.[10] The administration of both furosemide and electrolyte-free water will meet the therapeutic goal. The estimated volume of total body water is 51 liters (0.6×85). The retention of 1 liter of 5 percent dextrose is estimated to decrease the serum sodium concentration by 3.0 mmol per liter ($[0-156] \div [51+1] = -3.0$). To reduce the serum sodium concentration by 6.0 mmol per liter over a period of eight hours, 2.0 liters of 5 percent dextrose will be infused at a rate of 250 ml per hour. This estimated reduction will be counteracted by ongoing renal and extrarenal hypotonic fluid losses. Although allowance for the fluid losses, but not the sodium losses, must be considered, the patient's expanded extracellular-fluid volume calls for great caution in administering fluids. Thus, the fluid prescription will require adjustments based on close monitoring of the patient's clinical status and serum sodium concentration.

Hypernatremia with concurrent renal failure and volume overload poses a special management problem. Since diuretics cannot be relied on to reduce the expanded extracellular-fluid volume, hemodialysis, hemofiltration, or peritoneal dialysis must be used.

Common Errors in Management

Isotonic saline is unsuitable for correcting hypernatremia. Consider a 50-year-old man with a serum sodium concentration of 162 mmol per liter and a body weight of 70 kg (estimated volume of total body water, 42 liters [0.6×70]). The retention of 1 liter of 0.9 percent sodium chloride will decrease the serum sodium concentration by only 0.2 mmol per liter ($[154-162] \div [42+1] = -0.2$). Although the sodium concentration of the infusate is lower than the patient's serum sodium concentration, it is not sufficiently low to alter the hypernatremia substantially. Furthermore, ongoing hypotonic fluid losses might outpace the administration of isotonic saline, aggravating the hypernatremia. The sole indication for administering isotonic saline to a patient with hypernatremia is a depletion of extracellular-fluid volume that is sufficient to cause substantial hemodynamic compromise. Even in this case, after a limited amount of isotonic saline has been administered to stabilize the patient's circulatory status, a hypotonic fluid (i.e., 0.2 percent or 0.45 percent sodium chloride) should be substituted in order to restore normal hemodynamic values while correcting the hypernatremia. If a hypotonic fluid is not substituted for isotonic saline, the extracellular-fluid volume may become seriously overloaded.

Extreme care must be taken to avoid excessively rapid correction or overcorrection of hypernatremia, which increases the risk of iatrogenic cerebral edema, with possibly catastrophic consequences. Selecting the most hypotonic infusate that is suitable for the particular type of hypernatremia ensures the administration of the least amount of fluid. Appropriate allowances for ongoing fluid losses must be made to prevent serious deviations in either direction from the targeted serum sodium concentration. Scrupulous adherence to these management guidelines should help prevent such complications. Most important, the fluid prescription should be reassessed at regular intervals in the light of laboratory values and the patient's clinical status.

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