Hyponatremia and Hypernatremia

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Introduction

This chapter is divided into 2 sections: the major concepts concerning the physiology of sodium (Na^+) and water to provide a basis for understanding dysnatremia, followed by the clinical approach to patients with hypo- or hypernatremia. This approach at times begins with therapy rather than diagnosis, if one anticipates that the dangers for the patient are imminent and/or preventable. Following a consideration of emergency issues, a plan is constructed for investigation and longer term treatment. Case examples are used to illustrate major points.

Synopsis of the Physiology of Sodium and Water

This section will explain in more detail the forces that regulate the movement of electrolyte-free water (EFW) across cell membranes; how the distribution of fluid between the 2 major compartments of the extracellular fluid (ECF), the vascular and interstitial space, is regulated; and to emphasize that the volume of the intracellular fluid (ICF) compartment is reflected by the plasma Na^+ concentration (Na^+) for the most part, because the number of particles inside most cells does not change by an appreciable amount.

Composition of Body Fluids

Water usually accounts for 50 – 70% of body mass. It is not possible to relate total body water (TBW) to body weight by a single number because the relative proportion of fat and skeletal mass, the components of body mass with little water, are not constant. Women tend to have a higher proportion of fat and therefore a lower water content per body mass (50% body weight vs. 60% for males). The elderly also tend to have a relatively lower water content because of their high proportion of skeletal to muscle mass. Infants, on the other hand, have a higher proportion of water (70%) due to their smaller proportion of adipose tissue.

TBW is contained in 2 main compartments, the ICF and the ECF. The ICF is twice as large as the ECF compartment (Figure 1). The ECF consists of plasma fluid (4% of body weight) and interstitial fluid (16% of body weight). In certain disease states, excess fluid accumulates in the interstitial space of the ECF, resulting in edema, ascites, and/or a pleural effusion.

Water crosses cell membranes rapidly through aquaporin-1 (AQP-1) water channels in the cell membranes (Table 1) until the osmolality is equal on both sides of the membrane [1]. Not all materials dissolved in water disperse equally in the ICF and ECF because of differences in permeability, the presence of transporters, and/or active pumps that regulate their distribution. The volume of each

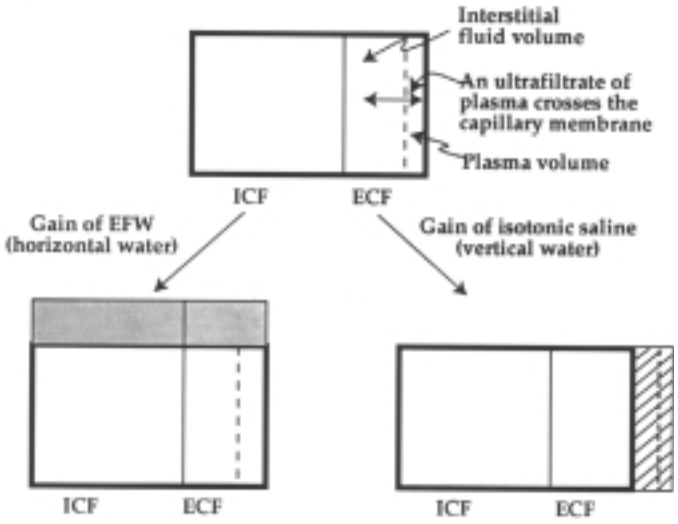

Figure 1. Body water. The rectangle in bold represents the body fluid compartments; the solid, thin, vertical line represents the membrane separating the ICF and ECF compartments; dashed, thin, vertical line separates the vascular and interstitial compartments. When there is a gain of EFW (bottom left), this water distributes in the ICF and ECF in proportion to their existing volumes (depicted by the horizontal, shaded rectangle above these normal compartments). It expands both volumes and therefore it leads to hyponatremia. In contrast, when there is a gain of isotonic saline, only the ECF volume expands (bottom right); this is depicted by the vertical, hatched rectangle. There is no change in the plasma [Na^+] or the ICF volume. Reproduced with permission [54].

compartment depends on the content of the predominant particles that are largely restricted to that compartment. Therefore, the content of Na^+ and its attendant anions in the ECF compartment determine its volume, since not only is the permeability of the cell membranes to Na^+ relatively low compared with that to K^+, but also any additional Na^+ that enters the cell is actively transported out of that cell by the enzyme Na^+-K^+-ATPase [2]. Likewise, the content of K^+ in the ICF compartment largely determines its volume. Under normal conditions, it is believed that there are roughly twice as many particles in the ICF compared to the ECF, and therefore the ICF volume is twice as large as that of the ECF (Figure 1). Some particles cross cell membranes rapidly, either via a transporter (urea) [3–5] or by diffusion (alcohol). Since their concentrations are virtually equal in the ECF and ICF of most cells they do not contribute to the "effective" osmolality or tonicity in these compartments.

The major factor responsible for water movement into cells is intracellular potassium (K^+) retention [6]. One reason for the retention is that the ICF anions are predominantly large macromolecular anions (organic phosphates) restricted to that compartment. Although these macromolecules do not exert a large osmotic pressure due to their small number, each of them bears a large number of anionic charges. Since the ICF macromolecules are largely organic phosphate esters (e.g. ATP, creatine phosphate, RNA, DNA, phospholipids) and are essential for cell function, only small net changes in their content occur in most cells. It follows that the total number of ICF particles is relatively fixed in most cells [7]. Therefore, changes in the par-

Table 1. Channels Influenced by AVP in the Nephron

I. Water channels	Most important location	Regulation by AVP
AQP-1 (also called CHIP-28)	Many cells; (e.g. proximal convoluted tubular cells)	None
AQP-2	Luminal or vesicle membranes of late distal nephron cells.	Activated, inserted, and synthesis increased.
AQP-3	Basolateral membrane of late distal nephron cells.	None
AQP-4	Basolateral membrane of late distal nephron cells.	None
II. Urea transporters (UT)		
UT	Descending thin limb of the loop of Henle and the descending vasa recta.	None
VRUT	Luminal membrane of late IMCD cells.	Yes.

AQP: aquaporin, UT: urea transporter (not vasopressin-reponsive), VRUT: vasopressin-reponsive urea transporter

ticle/water ratio in the ICF largely reflect a change in the intracellular water content. The particle/water ratio must be equal in the ECF and the ICF compartments because of the large magnitude of the osmotic pressure (100-fold greater than the mean arterial pressure). Thus, the ECF [Na^+] reflects the ICF volume in an inverse fashion in most cells, because Na^+ (and its attendant anions) accounts for virtually all of the "effective" osmolality of the ECF compartment. In contrast, brain cells can defend against large changes in their water content by varying the number of particles in their ICF compartment. This is termed regulatory volume control [8]. One mechanism used to return a swollen brain cell toward its original volume is to extrude electrolytes, which involves decreasing the content of K^+ (and usually chloride (Cl^-)) inside the cell. Another mechanism is to extrude small organic molecules such as myoinositol and other alcohols, taurine, and/or amino acids [9]. It is also possible that these osmotically-active particles are inactivated by binding rather than exrusion [10, 11]. Likewise, shrunken cells are returned toward their original volume by the influx of ions, typically Na^+. It is also possible to increase the number of small organic particles, such as amino acids or taurine [9].

Distribution of Fluid Across the Capillary Membrane

Factors controlling ultrafiltrate movement across the capillary membrane are shown in

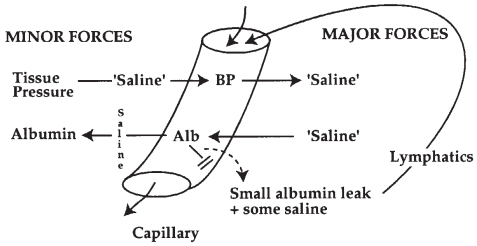

Figure 2. Events at the capillary membrane. The tubular structure is a capillary. The major outward-driving force is the capillary blood pressure and the major inward-driving force is the COP which is largely due to the effects of albumin (alb).

Figure 2. The major outward (vascular to interstitial) driving force is the hydrostatic pressure difference. When this hydrostatic pressure difference increases, as in venous hypertension (e.g. congestive heart failure (CHF)), more fluid moves from the vascular to the interstitial compartment. The major inward (interstitial to vascular) driving force is the colloid osmotic pressure (COP) difference. This is principally due to the concentration of albumin and its net anionic valence (Donnan effect). Since the intravascular compartment has a much higher concentration of albumin compared to the interstitial compartment, the COP causes fluid to move into the vascular space. When the concentration of albumin in plasma is very low, there may not be enough inward driving force and therefore the interstitial volume expands. Moreover, if capillaries become more permeable to albumin in a local area, edema fluid will accumulate. The final important component of the system is the lymphatics by which interstitial fluid is returned to the venous system.

The absolute pressure difference in mm Hg (hydrostatic pressure and COP) across a given capillary membrane is small but becomes a large force when the total capillary bed is considered. Therefore, another important factor here is the number of capillaries being perfused at any one time. If more are perfused, fluid can shift from the vascular to the interstitial compartment. If this flow exceeds lymphatic drainage, the vascular volume will be low. Since the interstitial fluid volume is so much larger than the vascular volume, any time one detects interstitial space expansion (edema), the patient will always have ECF volume expansion, even if the vascular volume may be reduced (e.g. hypoalbuminemia in patients with the nephrotic syndrome).

External Balances for Water

When a normal subject ingests EFW, it mixes with all body fluids. Two-thirds enters the ICF in steady state, while one-third remains in the ECF because water moves to osmotic equilibrium (Figure 1); thus, there is swelling of cells and hyponatremia.

Control of Water Intake

Thirst is stimulated by an increased tonicity. Particles like urea are not involved because they are not restricted to the ECF. Contraction of ECF volume is also a stimulus to thirst, but it is not a powerful one. Here, elevated levels of angiotensin II (Ang II) may act as a signal [13]. Other factors unrelated to a need for water may also stimulate water intake (e.g. dryness of the mouth, habit, social interactions). The major inhibitors of thirst are hypotonicity and, to a lesser degree, ECF volume expansion.

Control of Water Excretion

To return to steady state, the body must detect that there is a surplus of EFW (have a

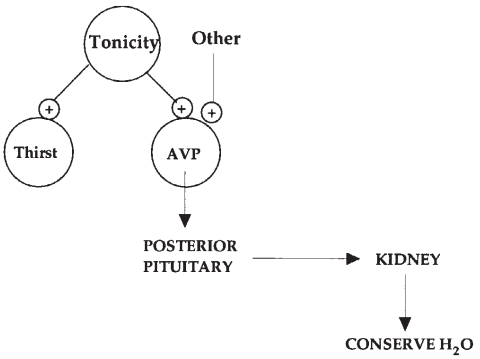

Figure 3. Control of the release of AVP and its actions on the kidney. For details, see text. The three circles represent the hypothalamic sensory system. The primary sensor is a group of cells that detect a change in their volume in response to a change in the "effective" osmolality of plasma (tonicity receptors). These cells are linked to other cells that control the intake of water (thirst center) and others that are responsible for the release of AVP. Other factors such as the "effective" circulating volume and afferent stimuli such as pain, nausea, anxiety, as well as a number of drugs also influence the release of AVP independent of the tonicity receptor influences.

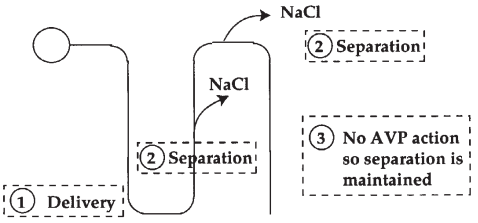

Figure 4. The excretion of dilute urine. The major structure is a stylized nephron. The numbers in the ovals represent the 3 major processes: the delivery of isotonic saline to the thick ascending limb of the loop of Henle (delivery, point 1), active resorption of NaCl from the thick ascending limb of the loop of Henle and in more distal nephron segments (separation, point 2) which generates EFW, and prevention of the reabsorption of EFW in more distal nephron segments because of a lack of AVP (maintain separation due to the absence of AQP-2 in the luminal membrane, point 3).

sensor), send a message to the kidney, and then direct the kidney to separate this EFW from its electrolytes (Na^+ salts) so that only the excess EFW can be excreted. The steps involved are as follows:

- *Sensor*: Tonicity receptors located in specialized cells in the anterior hypothalamus detect changes in cell volume [14]. This center is linked to both an area that drives thirst and another that releases arginine vasopressin (AVP) (Figure 3).
- *Messages*: Swelling of the tonicity receptor sends a message to the thirst center to diminish water intake and to the supraoptic nucleus to suppress the release of AVP. This absence of AVP translates into a message to the kidneys to excrete as much EFW as possible.
- *Renal events*: In the kidney, saline is filtered and some Na^+ and Cl^- are reabsorbed without water in the thick ascending limb of the loop of Henle and the distal nephron (Figure 4). The remaining EFW is excreted, because the luminal membrane of the distal nephron has a low permeability to water without AVP to insert aquaporin-2 (AQP-2) water channels (Table 1).

Excretion of a Dilute Urine

Excretion of EFW requires 3 steps: (1) delivery of Na^+, Cl^-, and water to distal diluting sites; (2) reabsorption of these ions without water (desalination); (3) ensuring that this EFW traverses the remainder of the distal nephron without being reabsorbed (maintenance of desalination) (Figure 4).

There are several nephron sites where Na^+ and Cl^- are reabsorbed, but water is not. The most important of these sites is the thick ascending limb of the loop of Henle. Other segments include the early distal convoluted tubule (DCT) (sparingly permeable to water

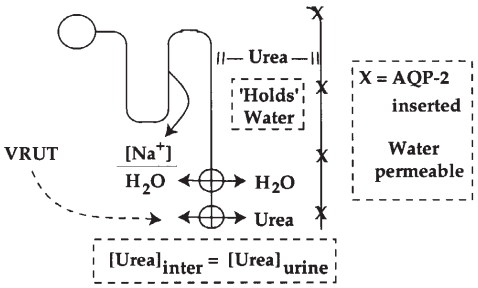

Figure 5. Formation of concentrated urine. For details, see text. There are 2 key elements operating at the renal level to excrete a concentrated urine. First, the "effective" osmolality of the medullary interstitial compartment must rise (this is represented as the Na^+/H_2O ratio in the interstitial compartment). Most important here is the active resorption of NaCl in the thick ascending limb of the loop of Henle. Second, water must be permeable across the luminal membranes of the late distal nephron (actions of AVP to insert AQP-2). The concentration of urea is elevated in the inner medullary interstitium largely because of actions of AVP to make urea permeable (VRUT is inserted) and a high concentration of urea in the urine.

even if AVP is present), the late DCT, and the collecting ducts (permeable to water in the presence of AVP).

Excretion of a Concentrated Urine

AVP action and an intact renal medulla are required to excrete a concentrated urine (Figure 5). The release of AVP from the posterior pituitary gland is stimulated by a rise in tonicity of body fluids and also by stimuli unrelated to tonicity (Figure 3) [15]. In the absence of water intake, the tonicity of body fluids rises because of ongoing EFW loss via the skin and the respiratory tract. This causes cells to shrink, particularly the tonicity receptor cells, which then causes thirst and AVP release.

AVP binds to its V_2 receptor on the basolateral membrane of cells of the late DCT and the collecting ducts, resulting in reabsorption of EFW. Three steps act to achieve this effect: the activation of AQP-2 water channels, their insertion in the luminal membrane, and the longer-term effect, the synthesis of more AQP-2 channels (Table 1) [1]. Most of the EFW is reabsorbed in the cortex when AVP acts [16]. To achieve this reabsorption, the "effective" osmolality of the interstitial fluid must exceed that of the lumen. This higher interstitial osmolality is due primarily to the active reabsorption of Na^+ and Cl^- in the thick ascending limb of the loop of Henle [16 – 18]. Thus, the passive transport of water down an osmotic difference is enhanced. As a result, a hyperosmolar urine is excreted and EFW is conserved.

Urea also contributes to the total osmolality of the interstitial fluid in the inner medulla and in the urine. In fact, it constitutes close to half the total osmolality in these locations in subjects who consume a typical Western diet. Nevertheless, if urea is permeable across the inner medullar collecting ducts (IMCD) because of the insertion of the vasopressin-regulated urea transporter (VRUT) [4, 5], it should not contribute to EFW conservation, a point illustrated in data from the rat [19]. Therefore, we prefer to think of the urine in "effective" osmolality terms rather than in total osmolality terms [20, 21].

Since one needs a hyperosmolar medullary interstitium to excrete a hyperosmolar urine, one cannot excrete a very concentrated urine in disease states where the medullary interstitium is damaged, regardless of the action of AVP.

External Balance for Na^+

People on a typical Western diet consume roughly 150 mmoles of NaCl daily. To remain in balance, 150 mmoles of NaCl must be

excreted daily. Thus, the Na^+ that was ingested must be sensed, the appropriate message sent to the kidney, and the reabsorption of filtered Na^+ in the kidney inhibited so that only the extra NaCl, and not water, will be excreted.

- *Sensor*: When NaCl is retained, the ECF volume expands. The most important component of the ECF is the "effective" circulating volume. Hence, baroreceptors in the arterial and central venous vessels detect changes in the "effective" circulating volume.
- *Messages*: The message of an increased "effective" circulating volume is delivered by renal nerves and hormones. Physical and hemodynamic factors also modulate the rate of reabsorption of Na^+ by the kidney.
- *Renal events*: In a normal adult, close to 27,000 mmoles of Na^+ are filtered each day. Of this large quantity, only a very small amount (150 mmoles, or about 0.5% of the filtered daily load) must be excreted to maintain balance for Na^+. Hence, Na^+ excretion is very tightly regulated, largely by changes in its reabsorption [22 – 24]. The first step required for the kidney to reabsorb Na^+ from the lumen is to create a driving force for the movement of Na^+ into the tubular cells. This is accomplished by lowering the $[Na^+]$ in the ICF of tubular cells, the result of the actions of the Na^+-K^+-ATPase in the basolateral membrane [2]. This transport system pumps 3 Na^+ out while transporting 2 K^+ into these cells. The Na^+-K^+-ATPase also creates an additional driving force for Na^+ reabsorption by creating a net negative voltage inside the cell. Since the luminal membrane is impermeable to Na^+, the second step required for the reabsorption of Na^+ is the insertion of specific transporters or Na^+ channels into this membrane. These transporters are specific for each nephron segment.

Na^+ Handling in the Proximal Convoluted Tubule (PCT): Of the 27,000 mmoles of Na^+ filtered each day, close to 18,000 mmoles (67%) are reabsorbed in the PCT. Co-transporters, e.g. glucose, and antiporters, e.g. H^+ on the Na^+/H^+ exchanger (NHE-3), are involved in these transport events. Electroneutrality is maintained by the reabsorption of the anions Cl^- and HCO_3^-. Since the luminal membrane here is permeable to water, the osmolality of the fluid leaving the PCT lumen is the same as that of the ECF. Ang II stimulates the reabsorption of $NaHCO_3$ in the PCT [25]. Water moves to osmotic equilibrium, thus raising the $[Cl^-]$ within the lumen. This creates a concentration difference for Cl^- which favors its passive reabsorption; Na^+ ions follow for electroneutrality.

Na^+ Handling in the Loop of Henle: Of the remaining 9 000 mmoles of Na^+ exiting the PCT lumen, 6 000 mmoles are reabsorbed in the loop of Henle. NaCl is actively transported by the Na^+-K^+-2 Cl^- co-transporter using the driving force (low $[Na^+]$ in the ICF) created by the Na^+-K^+-ATPase. The absolute reabsorption of Na^+ varies with delivery, and net reabsorption is stimulated by the action of AVP in the medullary thick limb. In the thick ascending limb, water reabsorption is negligible. Thus, the fluid exiting this nephron segment is hypotonic to plasma.

Na^+ Handling in the DCT: Close to 2 000 mmoles of the remaining 3 000 mmoles of Na^+ are reabsorbed in the DCT. Since the DCT is not permeable to water, EFW is created. Na^+ is reabsorbed with Cl^-, driven by the transepithelial $[Na^+]$ gradient across the luminal membrane of the DCT. The ion transporter

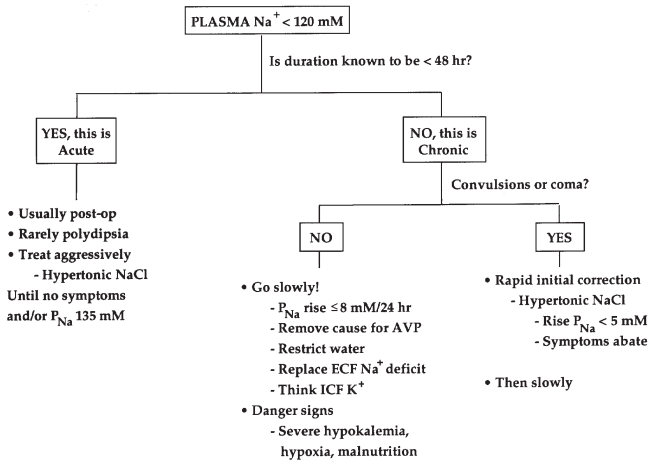

Figure 6. Approach to the patient with hyponatremia. Pseudohyponatremia and translocation type of hyponatremia should be ruled out. This figure should be examined together with Tables 3 and 4 for a more complete lists of conditions. Reproduced with permission [55].

is the Na^+-Cl^--co-transporter, which may be inhibited by thiazide diuretics. A molecular defect in this transporter causes Gitelman's syndrome (see chapter I-2, Potassium).

Na^+ Handling in the Collecting Duct: Close to 700 mmoles of the remaining 1 000 mmoles of Na^+ are reabsorbed in the cortical collecting duct (CCD) through a specific Na^+ ion channel [26]. Mineralocorticoids lead to greater opening of this channel [27], while amiloride, a K^+-sparing diuretic, inhibits it. The medullary collecting duct (MCD) reabsorbs about 150 mmoles of the remaining 300 mmoles of Na^+ delivered, so that 150 mmoles of Na^+ can be excreted to stay in Na^+ balance. In this segment, a high transepithelial [Na^+] gradient is maintained. Atrial natriuretic peptide (ANP) acts here to decrease the reabsorption of Na^+ [28], in ECF volume expansion. In contrast, during ECF volume contraction, the absence of ANP causes almost all of the Na^+ delivered to be reabsorbed.

Clinical Approach to the Patient with a Dysnatremia

General Aspects about a Patient with Hyponatremia

Is there a Major Threat to the Life of the Patient related to Hyponatremia?

The main danger in the patient in whom hyponatremia developed in < 48 hours (acute hyponatremia) is swelling of brain cells which may lead to seizures, herniation of the brain and death (Figure 6, Tables 2 and 3). In contrast, in the patient who becomes hyponatremic over a much longer time period (chronic hyponatremia), the main danger is an overly rapid rate of shrinkage of brain cell volume as a result of aggressive correction of hyponatremia. This may result in the development of an osmotic demyelination syndrome (ODS) and loss of higher cerebral functions [29]. It is important to remember that the acute discovery of a chronic condition does not make it an acute disorder.

Table 2. Overview of Hyponatremia

Type of hyponatremia	Clinical Setting	Main danger	Treatment
Acute (documented < 48 hour).	Usually postoperative.	Brain cell swelling.	Hypertonic saline to raise [Na^+] to 130 mM
Chronic	Many causes.	Osmotic demyelination.	Rise in the plasma [Na^+] should not be > 8 mM/day

Table 3. Classification of Hyponatremia

1. Acute hyponatremia (< 48 hour duration):
   a) Source of EFW:
      – Exogenous (IV or oral)
      – Endogenous = Desalination of IV or body fluids
         – Acute postoperative period
         – Cerebral salt wasting
         – Thiazide diuretics in an edematous patient
         – Giving isotonic saline to a patient with SIADH.
   b) Reason for AVP being present
      – Low "effective" ECF volume
      – Pain, anxiety, nausea, psychosis
      – Endocrine reasons (adrenal, thyroid, pituitary)
      – Metabolic disorder (e.g. porphyria)
      – Drugs
      – None of the above, see Table 5.
2. Chronic hyponatremia:
   a) Source of EFW is always needed
      – usually not the most important component of the problem.
   b) Reason for AVP (see above).

Has a Shift of Water Occurred across Cell Membranes in a Patient with Hyponatremia?

NO, the ICF volume did not change: This is the case when an isosmolar solution containing solutes other than Na^+ are added and these new solutes were retained primarily in the ECF compartment, e.g. retained lavage solution during a transurethral resection of the prostate (TURP). An example is provided in Table 4.

YES, the ICF volume has decreased in size (shrunken cells): This is the case when the solution added had both an osmolality greater than that of the ECF and the solutes that were added are retained in the ECF compartment (e.g. hyperglycemia or administration of a bolus of mannitol).

YES, the ICF volume has increased in size (swollen cells): This is the case when the solution added had an "effective" osmolality lower than that of the ECF (the addition of EFW) or hypotonic sorbitol or glycine (e.g. during a TURP) and/or the solutes added were distributed in the ECF and ICF compartments (e.g. urea or ethanol).

What is the Pathophysiology of Hyponatremia?

Two major factors should be considered and each must be analyzed independently.

There is a source of EFW: This is the more important factor in patients with acute hy-

Table 4. Comparison of EFW and isosmotic mannitol on the degree of hyponatremia. Examples are provided to illustrate the effects of retaining 3 L of EFW or 3 L of half-isotonic mannitol on the plasma [Na^+] and the volumes of the ICF and ECF. We assumed that the patient has 30 L of total body water in each case, 2/3 of body water is in the ICF compartment, mannitol will be excreted at a concentration of 300 mM during an osmotic diuresis [51, 53]. Notice the degree of change in the plasma [Na^+] when mannitol is excreted, a time with no change in the volume of the ICF compartment. This illustrates the problems relating the plasma [Na^+] and the ICF volume in translocational hyponatremia.

Parameter		Normal	Gain 3 L	Mannitol	
		Values	EFW	Gain 3 L	Excrete mannitol
Total body water	L	30	33	33	31.5
– ICF volume		20	22	21	21
– ECF volume		10	11	12	10.5
Plasma [Na^+]	mmM	140	127	114	133
– Change	mmM	0	– 13	– 26	– 7

ponatremia. In acute hyponatremia, the condition must be present for < 48 hours. As mentioned above, the major concern is brain swelling because the brain is enclosed by a rigid structure, the skull.

AVP is acting: This is the more important factor in patients with chronic hyponatremia. In the short term, one is primarily concerned with the fact that AVP might disappear and lead to too rapid a rate of correction of the hyponatremia and thereby, the development of ODS. In the long term, one is concerned with the underlying reason for AVP excess. Chronic hyponatremia includes all cases where there is a reasonable doubt about the plasma [Na^+] in the past 48 hours. If the patient is symptomatic (e.g. seizures) the worry is brain swelling and treatment is aggressive initially. If the patient is not severely symptomatic, the worry is the ODS with too rapid a rise in the plasma [Na^+].

Clinical Approach to the Patient with Acute Hyponatremia

Acute hyponatremia (developing over < 48 hours) implies insufficient time for swollen brain cells to shrink their volume back to a normal size. Due to the physical restriction imposed by the cranial vault, intracranial pressure (ICP) rises causing central nervous system symptoms, which may become serious (seizures or coma) or devastating (respiratory arrest and irreversible brain damage).

In the patient with acute hyponatremia, the emphasis at the bedside is on the source of EFW. The cause for the release of AVP is usually obvious (Table 4). The most common setting for acute, potentially life-threatening hyponatremia, is in the intra- and postoperative setting, and thus most of these cases occur in hospital. There are 3 obvious sources of EFW in this setting: (1) the administration of

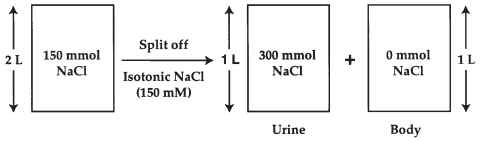

Figure 7. Desalination type of hyponatremia. The rectangles represent 1 L volumes. The [Na^+] in each L is shown in the rectangle. The left rectangle represents 2 L if IV infusions. The first rectangle to the right of the arrow represents the hypertonic urine, and the second rectangle to the right of the arrow represents the 1 L of EFW generated and retained in the body due to AVP actions. Reproduced with permission [55].

glucose in water (D_5W), or hypotonic saline as intravenous fluids (virtually always occuring in the perioperative period); (2) the intake of ice-chips or sips of water (also perioperative period); (3) the generation of EFW from the kidney excreting urine that is hypertonic to the infusate (or to body fluid in the absence of intravenous infusions [30]) (Figure 7).

Prevention: The best way to avoid acute postoperative hyponatremia is to avoid giving solutions that are hypotonic to the urine if polyuria is present, or hypotonic to body fluids in the oliguric patient. In addition, isotonic fluids should only be given to maintain systemic hemodynamics during surgery and to replace losses if they occur. One should be very suspicious of a "good" urine output because this might be hypertonic to the infused solutions and generate EFW (Figure 7). The plasma [Na^+] should be monitored in settings associated with AVP release (Table 4), particularly in patients who excrete more than 1 – 2 L of urine/day. Finally, caution should be used with the volume of fluid given to a small patient, as a large volume of fluid in a small patient translates into more EFW generation if the urine is hypertonic to the fluids administered. This is especially important in menstruous females, in whom acute hyponatremia may be more dangerous [31].

Emergency therapy: The immediate goal of therapy is to shrink the expanded ICF volume of the brain sufficiently to curtail the serious CNS symptoms. If hyponatremia is severe (< 120 mM) or symptoms are present, one should administer hypertonic saline until the plasma [Na^+] is close to 130 mM. When calculating the amount of Na^+ required, one must assume that its volume of distribution behaves as if the Na^+ will be dissolved in TBW, since the cell membrane is permeable to water, but not to Na^+ [32]. To clarify these points, consider the following illustrative case.

– *Case example:* Hyponatremia (plasma [Na^+] 120 mM) developed in a 50-kg person 24 hours after surgery; a seizure has just occurred. Therefore, the initial aim of therapy is to shrink the size of brain cells over 1 – 2 hours to the pre-seizure level. A reasonable target is to raise the plasma [Na^+] by 5 mM over the next 1 – 2 hours. In order to achieve this, 125 mmoles of Na^+ should be administered, given a TBW of 25 L (50% of body weight). Since 1 L of 3% saline contains close to 450 mmoles Na^+, 0.3 L of this solution should be administered. After the seizure is controlled, the rate of infusion may be slowed, with the goal of raising the [Na^+] to 130 mM. Careful observation is required to avoid the development of pulmonary edema.

Maintenance Therapy: Once the plasma [Na^+] has been raised to 130 mM, one should ensure that it does not fall any further. The tonicity balance approach (Figure 8) uses 2 general strategies to prevent a further fall in sodium in a patient who is excreting a large volume of hypertonic urine.

– Input: If the input is equal to the output with respect to Na^+, K^+, and water, there will be no change in the plasma [Na^+]. Since hypertonic saline is being excreted,

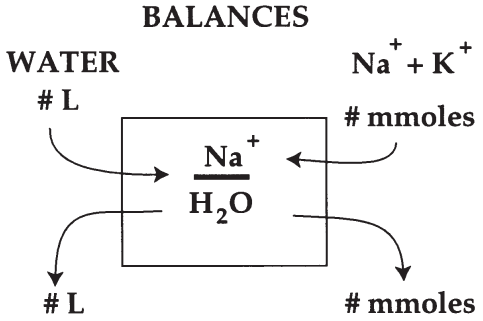

Figure 8. Tonicity balance. The rectangle represents all body compartments. To calculate a tonicity balance, one must have separate balances for water and $Na^+ + K^+$. The data can predict how the $[Na^+]$ in plasma should change; this should be compared to measured values. Reproduced with permission [55].

the same volume and the same composition of hypertonic saline must be administered.

– Output: Here the aim is to lower the concentration of Na^+ and K^+ ($[Na^+ + K^+]$) in the urine so that isotonic fluids can be administered. If the $[Na^+ + K^+]$ in the urine is very high [30], one can render it isotonic with the administration of a loop diuretic (e.g. furosemide) [33, 34] or an osmotic diuretic (e.g. urea) [35]. Isotonic intravenous fluids should be given at the same rate as that of the urine output. Once the reason for the release of AVP is no longer present, this therapy will not be required. The patient will begin to excrete dilute urine and hence the plasma $[Na^+]$ will rise [30].

Specific Examples

Acute hyponatremia in females: Most commonly, this follows otherwise uneventful gynecological surgery which leads to the sustained release of AVP for a number of reasons, such as pain, anxiety or drugs [31]. The ill-advised infusion of D_5W, the most common source of EFW in this setting, exacerbates the problem. Even isotonic saline can present the body with a large infusion of EFW [30] (Figure 7). The severity of hyponatremia may be worsened if the volume of fluid given is not scaled down to body size. This form of acute hyponatremia leads to brain cell swelling and rarely, death due to high ICP in some patients. A quantitative example is provided in Table 4.

Acute hyponatremia in males: The list of causes of acute hyponatremia in males reflects the type of surgical procedure they are likely to undergo. The most common surgery for males is TURP [36]. The main reason for hyponatremia in this setting is that large volumes of half-isotonic solutions of organic compounds are used to lavage the prostatic bed, some of which may be absorbed. The development of hyponatremia becomes clear when the absorbed fluid is divided into its two constituent parts (Table 4).

– *Gain of osmol-free (and electrolyte-free) water:* This simple EFW gain causes cells to swell, but it is not the major cause for the hyponatremia (fall of 7 mM in the plasma $[Na^+]$ in the example provided in Table 4).

– *Gain of isosmolar fluid:* Solutes such as mannitol, glycerol, or glycine distribute in the ICF compartment at a slow rate [37]. When they remain in the ECF, they cause hyponatremia because these solutions are Na^+-free. This transient form of hyponatremia is not associated with a change in brain cell volume, and so does not pose a threat of brain herniation [38]. A low plasma osmolality in the setting of acute hyponatremia following a TURP poses a threat of brain cell swelling. If that osmolality is close to normal, one should not be alarmed with the severity of the hyponatremia and the rapidity of its correction (Table 5). The symptoms

Table 5. Causes of High AVP Levels in Patients with Hyponatremia

1. AVP release in response to physiologic stimuli:
   – Low "effective" circulating volume
      – ECF volume depletion
      – Blood loss
      – Hypoalbuminemia
      – Low cardiac output.
   – Excessive pain, nausea, vomiting. or anxiety.

2. AVP release without a physiologic stimulus:
   – CNS or lung lesions.
   – Neoplasms and granulomas such as tuberculosis.
   – Metabolic lesions such as acute intermittent porphyria.
   – Administration of agents that simulate AVP
      – DDAVP (e.g. treatment for diabetes insipidus or urinary incontinence)
      – Oxytocin for labor induction.
   – Drugs that augment or stimulate AVP release:
   – Examples include nicotine, morphine, clofibrate, tricyclic antidepressants, antineoplastic agents, (probably via nausea and emesis), anticonvulsants such as tegretol.
   – Drugs that promote the actions of AVP on the kidney by increasing cyclic AMP levels or augmenting its bioactivity:
      – Examples include oral hypoglycemics (e.g. chlorpropamide), methylxanthines (e.g. caffeine, aminophylline), analgesics that inhibit prostaglandin synthesis (e.g. aspirin, non-steroidal anti-inflammatory drugs).

associated with hyponatremia when glycine is used as the lavage fluid during a TURP may be the consequence of hyperammonemia rather than swelling of cells of the brain [36].

Hyponatremia with primary polydipsia: Normally one cannot become hyponatremic simply from drinking EFW, because AVP will be absent and in this setting, normal kidneys can excrete close to 1 L of EFW/hour, more than almost anyone can drink and absorb [39 – 41]. Nevertheless, if there is a reason for AVP release, such as an appreciably low ECF volume, anxiety, pain, psychosis, or the intake of certain drugs (Table 4), the intake of EFW will result in hyponatremia [30].

Hyponatremia in an infant: Apart from unique disorders such as inborn errors, hyponatremia in this setting is most commonly due to a loss of Na^+ (e.g. diarrhea). This form of hyponatremia may be acute. AVP is released in response to the contracted ECF volume, and this leads to the retention of EFW that is ingested by the infant. If a hyponatremic infant is fed sugar water to rest the GI tract and avoid dehydration, this EFW will be retained. Thus, hyponatremia has 2 components: loss of Na^+ and gain of EFW. Its degree may be very severe. The 2 considerations for therapy include rapid re-expansion of the contracted ECF volume by infusing "isotonic to the patient" saline and avoidance of any further addition of EFW (this includes the generation of EFW by the kidneys if the rate of excretion of Na^+ were to rise while AVP is still acting, Figure 7).

Summary

– Do not give EFW to a subject with a plasma $[Na^+] < 138$ mM. Give a smaller volume if the patient is likely to have AVP released for nonosmotic reasons.
– Do not give more isotonic saline during surgery and in the acute postoperative time than is needed to maintain normal hemodynamics.
– Be careful if the urine output is larger than expected.
– Use a tonicity balance calculation to help understand the basis of hyponatremia and to plan therapy. Emphasis can be placed on changing the input or the output.

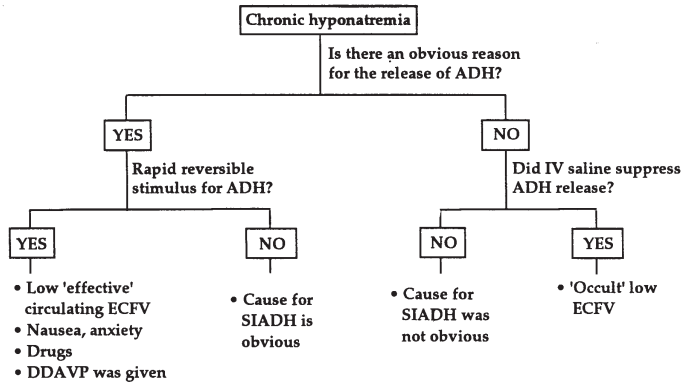

Figure 9. Steps to take in the patient with chronic hyponatremia. The focus in chronic hyponatremia is to determine why AVP is present. If the reason for the release of AVP is reversible, patients might be at risk of having a water diuresis if the release of AVP is suppressed – e.g. when their ECF volume is re-expanded. Reproduced with permission [55].

Clinical Approach to a Patient with Chronic Hyponatremia

Chronic hyponatremia is the most common electrolyte abnormality in hospitalized patients [42], but it rarely leads to significant symptoms (Figure 9). The patient with chronic hyponatremia is often identified by the determination of routine electrolytes, in which case the duration of the disorder is unknown. The fundamental issue here is that adaptive responses have had time to occur, the most important of which are in the brain. Brain cells have returned their volume virtually to normal (for review see [9]). The initial mechanism is the export of ions (K^+), providing that electroneutrality was not the result of the entry of Na^+ into their ICF (it is not clear which anion might be exported with K^+, but the defense of the ICF volume of cells of the brain would be most efficient if Cl^- were also exported from these cells). Over the next few days, organic molecules such as myoinositol, amino acids, and taurine are exported. Brain cells must reaccumulate solutes that were lost to achieve a normal ICF volume and composition; this provides the rationale for deciding the rate of correction of hyponatremia. The critical issue is that these cells, which have undergone volume regulation, are at risk of an acute decline in their volume if the plasma $[Na^+]$ is raised before these solutes are taken up. This is even more important if these cells do not have available organic osmolytes to re-establish their normal ICF osmole composition. For example, a patient with poor nutrition or a large deficit of K^+ may take longer to regain these intracellular organic osmolytes [43]. Correction of hyponatremia exceeding 6 – 8 mM/24 hours, can lead to the devastating neurologic syndrome, ODS [44].

Diagnostic Issues

To develop hyponatremia, a source of EFW (usually ingestion of water) coupled with a limitation to its excretion (release of AVP) must be present. Virtually everyone drinks EFW, so one need not dwell on this for diagnostic purposes unless the intake is very large. The diagnostic issue focuses on why the rate of excretion of EFW is so low. The challenge to the physician is to identify why AVP was released despite a low plasma "effective" osmolality (Table 5, Figure 9). The objective at the bedside is to determine whether AVP levels will decline rapidly, leading to an overly rapid rate of hyponatremia correction, thus predisposing the patient to ODS.

Several examples where the level of AVP might decline abruptly include chronic nau-

sea, vomiting, anxiety, and/or stress, or when desmopressin (DDAVP) is given to patients in a nursing home to minimize bed wetting. In addition, the apparent on-again, off-again release of AVP may be the result of a decreased "effective" circulating volume. When the "effective" circulating volume is low enough, AVP will be released, even if hyponatremia is present. This helps to defend the ECF volume at the price of an expanded ICF volume. Since thirst is also stimulated by a low "effective" circulating volume, both a source of EFW and the release of AVP to prevent its excretion are present. The problem is that a clinician may have great difficulty in deciding whether the "effective" circulating volume is contracted unless the changes are marked. One can use clues from the history. First, there may be excessive renal loss of Na^+. Its most common cause is the ingestion of a diuretic. Less often, renal salt wasting and/or an osmotic diuretic (e.g. glucose or urea) may cause excessive excretion of Na^+. In patients with renal salt wasting, examining the rate of excretion of K^+ may help determine the nephron site with defective handling of Na^+. A low rate of excretion of K^+ in the face of renal Na^+ loss and ECF volume contraction should suggest that there is a lesion in the CCD, for example a low aldosterone bioactivity. In contrast, a high rate of excretion of K^+ with renal Na^+ wasting suggests that an abnormal loss of Na^+ occurred in the PCT (usually with metabolic acidosis), the loop of Henle (as in patients with Bartter's syndrome), or the early DCT (as in patients with Gitelman's syndrome). Although one would expect a low rate of excretion of Na^+ and Cl^- when the ECF volume is low, there are notable exceptions to this rule. Na^+ may be excreted if there is a high rate of excretion of another anion such as HCO_3^- in the patient who has vomited recently. In this case, the excretion of Cl^- should be low. In contrast, if the loss of NaCl was due to diarrhea, the associated metabolic acidosis will cause a high rate of excretion of ammonium (NH_4^+) and because this NH_4^+ is excreted with Cl^-, the urine may be Cl^--rich but Na^+-poor (Table 6). Loss of Na^+ can also occur via nonrenal mechanisms. These are usually obvious (e.g through gastrointestinal tract or skin) and should be suspected when the urine is virtually Na^+-and/or Cl^--free *all* the time. The "effective" circulating volume is decreased either when the overall ECF volume is reduced or when the ECF volume is maldistributed so that there is insufficient volume in the "effective" vascular compartment, as in edema states (e.g. in patients with hypoalbuminemia). A second type of maldistribution occurs when the arterial volume is low and the venous volume is high, as when there is a primary decrease in cardiac function or venodilitation.

Table 6. Urine Electrolytes in the Differential Diagnosis of Hyponatremia. (These urine electrolyte levels do not apply to polyuric states.)

Condition	Urine Electrolyte Na^+	Urine Electrolyte Cl^-
– Vomiting		
Recent	High*	Low**
Remote	Low	Low
– Diuretics		
Recent	High	High
Remote	Low	Low
– Diarrhea or laxative abuse	Low	High
– Bartter's or Gitelman's syndrome	High	High

*High = Urine concentration > 15 mM, **Low = Urine concentration < 15 mM

Clinical Clues

Four laboratory tests might help indicate if the "effective" circulating volume is contracted.

- *Plasma [K^+]*: Either hypokalemia or hyperkalemia can suggest the reason for the release of AVP. When the ECF volume is low, release of aldosterone results in renal K^+ loss. This loss is especially high when volume and bicarbonate (HCO_3^-) delivery to the CCD are high. Therefore, hyponatremia associated with diuretics or vomiting should be suspected if hypokalemia and renal K^+ wasting are present. In contrast, patients who have hyponatremia and hypokalemia due to diarrhea may have a low rate of excretion of K^+ if their loss of K^+ occurred via the GI tract. Finally, in patients with Addison's disease (low aldosterone levels) and hyponatremia, hyperkalemia is usually present.

- *The plasma [HCO_3^-]*: The plasma [HCO_3^-] may be high in patients who have vomiting or diuretic-induced hyponatremia (metabolic alkalosis). In contrast, hyponatremia of hypoaldosteronism is generally accompanied by a mild fall in the plasma [HCO_3^-] to close to 20 mM, because of a low rate of excretion of NH_4^+ consequent to renal effects of hyperkalemia [45, 46].
- *The BUN*: In patients with the syndrome of inappropriate secretion of AVP (SIADH), the fractional excretion of urea increases, probably as a result of ECF volume expansion [47]. This together with dilution due to water retention and possibly a low protein intake results in a fall in the concentration of urea in plasma (BUN). In hyponatremia associated with a low "effective" circulating volume, there is a higher plasma urea level because the stimulus to AVP release (ECF volume contraction) leads to a fall in the GFR and an enhanced rate of reabsorption of filtered urea in the PCT.
- *The plasma urate level*: The plasma urate level may be quite low in patients with hyponatremia caused by SIADH. The mechanism is thought to be due to the expanded ECF volume in SIADH. If the ECF volume is contracted, more urate is reabsorbed and its level in plasma could rise.

Quantitative considerations: When AVP acts, the urine will contain very little EFW in patients who maintain their usual intake of salt. Nevertheless, to deduce what the anticipated changes are likely to be, one must examine the input and output, and perform a tonicity balance (Figure 8). The following examples illustrate these 2 points.

Example 1, emphasis on the source of EFW: Subjects on a normal Western diet consume 150 mmoles of NaCl and 50 mmoles of K^+, and excrete 1.5 L of urine a day. They remain in balance and their 24-hour urine [$Na^+ + K^+$] is 133 mM. Since the urine [$Na^+ + K^+$] can only rise to just over twice this value because of a limit set by medullary tonicity, positive balance for EFW can only be approximately 0.75 L/day. Said another way, it is difficult to have a large daily positive EFW balance, unless the intake of water increases appreciably and/or the intake of NaCl declines to a major extent.

Example 2, emphasis on the content of Na^+ in the ECF: An elderly woman consumes tea and toast. Her intake of EFW is not low because she drinks a large cup of tea by habit; however, her diet contains little $Na^+ + K^+$. To stay in balance, she must excrete urine with a very low [$Na^+ + K^+$]. If AVP is acting, the [$Na^+ + K^+$] in her urine can rise to close to 300 mM

[18]. Hyponatremia can develop quickly and now EFW will be generated rather than excreted (Figure 7). Hence, both the electrolyte and EFW intake, plus the capacity to have a high [$Na^+ + K^+$] in the urine, impact on the likelihood of developing hyponatremia and contribute significantly to its severity.

Clinical Settings for Chronic Hyponatremia

One first tries to identify patients with an "effective" circulating volume that is obviously contracted and those with SIADH, either from medications or a condition that may cause the release of AVP (Table 5).

SIADH: A persistently elevated level of AVP acts to limit the excretion of EFW. When EFW is ingested, much will be retained and cause hyponatremia. Initially, the ECF volume is expanded so Na^+ is excreted in the urine. Hence, the characteristic findings in steady state are hyponatremia, the absence of ECF volume contraction, and a urine which contains as much Na^+ and Cl^- as the patient is ingesting. A note of caution is needed here. Patients with SIADH who consume a low salt diet will have little Na^+ and Cl^- in their urine, so a high urine [Na^+] is not a requirement for this diagnosis. The urine osmolality exceeds the minimum value of 30 – 80 mosm/kg H_2O, which is the expected value if AVP is absent. Before establishing the diagnosis of SIADH in a patient with chronic hyponatremia, be sure that there is no reduction of the "effective" circulating volume. This might require an infusion of isotonic saline. When this is done, SIADH is ruled out if the urine osmolality declines to minimum values.

There are 4 subgroups of SIADH as shown by Robertson et al. [48]. The first subgroup is the patient with random high autonomous release of AVP. A common example is the patient with carcinoma of the lung. These patients represent 35 – 50% of those with SIADH.

The second subgroup is the patient with reset osmostat. These patients have normal regulation of the release of AVP, but it is controlled around a hypotonic setting. About 33% of patients with SIADH fall into this subcategory.

The third subgroup is the patient with failure to suppress AVP totally with hypotonicity. About 15% of patients will have SIADH in which the release of AVP is normal at a high tonicity of plasma, but not absent at low plasma tonicity.

The fourth subgroup consists of about 15% of patients with SIADH. They have no problems with the regulation of the secretion of AVP, but their kidneys are either overly sensitive to AVP, or there is a circulating AVP-like material present. Perhaps some of these patient have a very low delivery of Na^+ to the distal nephron. Because the IMCD has intrinsic permeability to water even in the absence of AVP [1], they can reabsorb water from the IMCD if their interstitial fluid compartment has a high "effective" osmolality. We have called this trickle-down hyponatremia [49].

Therapy for the Patient with SIADH

Treatment of the underlying illness is crucial, but beyond the scope of this discussion. We shall restrict our comments to the treatment rapidity of correction of hyponatremia.

– *Prevention*: Certain clinical situations are associated with chronic but reversible release of AVP (Table 5). These patients will be at risk for a more severe degree of

hyponatremia if they receive EFW, and are in danger of spontaneous excessive rapid rate of correction of their hyponatremia.

– *Active treatmen*t: Only in rare circumstances should the rate of correction of chronic hyponatremia be rapid, and then, only for a short period of time. Nevertheless, we start with rapid correction because it may be necessary in a medical emergency.

Rapid correction: Use aggressive treatment only for those patients whose symptoms are very serious (e.g. seizures or coma). In this setting, one wishes to shrink the size of brain cells to that present before onset of symptoms. In practice, this means that hypertonic saline should be given to raise the plasma [Na^+] to a level where the seizure activity is not present (usually a rise in serumNa of up to 5 mM). The amount of Na^+ without water to give is 5 mmoles/L of TBW. Nevertheless, do not let the rise in plasma [Na^+] exceed an overall 24-hour rate of 8 mM [44].

Caution: With an acute seizure, the plasma [Na^+] may rise by 10-15 mM because of an acute shift of water into muscle cells, so the plasma [Na^+] at the time of the seizure may be artificially elevated. Therefore, the plasma [Na^+] should not be raised by 8 mM above the first recorded plasma [Na^+] drawn immediately after a seizure.

Slow correction: The objective here is to choose a rate of correction with which virtually no patient is known to have developed ODS (< 8 mM/day) [44]. The rate of correction should be made even slower if the patient could have difficulty with the availability of K^+ and/or organic osmolytes (e.g. alcoholics, patients with hypoxia, malnutrition, or those with a catabolic state such as burn victim) [43].

Specific Emphasis for Therapy

We can identify 3 components which should be addressed in the patient with hyponatremia, each of which requires specific therapy. These will be discussed in the following paragraphs and then be applied to the management of 3 hypothetical patients.

– *Return the ICF volume to normal*: Cells have an excess of EFW which they must lose at a slow rate. This requires a negative balance for EFW. Hence, EFW input should be limited, and strategies should be employed to increase its loss.

– *Return the composition of the ECF to normal*: Most patients with SIADH have a near-normal ECF volume. Nevertheless, the ECF [Na^+] is lower than normal. Therefore, to maintain a normal ECF volume, when EFW is lost, there must be a positive balance for Na^+. By examining quantitative changes (Figure 8), one can appreciate the importance of the Na^+ deficit.

– *Return the composition of ICF to normal*: The issues regarding a surplus of EFW in the ICF compartment have been considered above; 2 remaining aspects are restorating the K^+ deficit, if needed, and restorating the organic osmolytes of the ICF of the brain. If a K^+ deficit was present, it should be replaced with KCl. In the ICF, KCl creates a positive balance for K^+ and a negative balance for Na^+ and H^+. In the ECF, there is a positive balance for Na^+ and Cl^-. Since the KCl is usually given in a hypertonic form, there will be a net gain of hypertonic NaCl in the ECF, a rise in natremia and an expanded ECF volume. If the ECF volume was normal to begin with, the final step is to facilitate the excretion of the extra ECF volume as "isotonic to the patient" NaCl. The time course needed to restore intracellular or-

ganic compounds lost in the development of hyponatremia is a very important consideration. An even slower rate of correction of hyponatremia is prudent when there is a hypokalemia in a patient who is malnourished or has an intensely catabolic state (e.g. burn victim), and/or hypoxia [43].

Case Examples

The following 3 cases are provided to emphasize that the first step in therapy might differ in individual patients with chronic hyponatremia.

- *Case 1, focus on the ICF volume:* You are asked to treat the hyponatremia in a 50-kg person with SIADH due to a tumor. Plasma [Na^+] is always approximately 126 mM and plasma [K^+] is 4.0 mM. No symptoms are attributable to hyponatremia. The ECF volume is normal and the patient consumes a usual diet (150 mmoles NaCl per day).
- *Discussion of Case 1:* There is no urgency here. This patient will need to lose close to 2 L of EFW (the plasma [Na^+] is decreased by 10% so, without a change in the number of particles in the ICF, the ICF volume would be expanded by 10% or 2 L, if the ICF volume in this patient is close to 20 L). The course for this therapy will be several days. The simplest approach is to reduce the intake of EFW to close to less than its rate of excretion. The deficit of NaCl in the ECF can be restored without supplement because the diet has an abundant amount of NaCl. If this therapy does not work, the next step would be to increase the excretion of EFW in the urine. The best way to increase the excretion of EFW is to add osmoles such as urea to force the excretion of water at a given high urine osmolality [35]. In general, the addition of 400 mmoles of urea (24 g) will cause the excretion of 1 L of EFW. Another strategy is to use a loop diuretic to cause the excretion of isotonic saline. In this case, replacing all the ions excreted without water will cause a loss of EFW [33, 34].
- *Case 2, focus on the ECF volume:* A 50-kg person who consumes a low salt diet had a thiazide diuretic prescribed for hypertension. Current symptoms are weakness, a lack of energy, and a feeling of light-headedness upon standing. The "effective" circulating volume is contracted on physical examination (blood pressure is now 135/70 mm Hg (previously160/90 mm Hg) and there is a 20 mm Hg postural drop in blood pressure). Hyponatremia (115 mM) and a low plasma [K^+] (3.4 mM) are present. Urine output is close to 1 L per day with diuretic use. What should the therapy be?
- *Discussion of Case 2:* For now, it is safe to ignore the ICF volume and its composition. The aim of therapy is to administer 1 to 2 L of "isotonic to the patient" saline to reexpand the ECF volume. However, there is a major potential risk in this patient. If the release of AVP was due to a low "effective" circulating volume, when this volume is re-expanded, secretion of AVP may cease and a large water diuresis could occur. If therapy is not changed, the plasma [Na^+] would now rise too rapidly, making ODS more likely. Therefore, AVP should be available at the bedside and be used if the patient excretes enough dilute urine to raise the plasma [Na^+] by more than 8 mM/day.
  One other point merits emphasis. Since the patient is consuming a low salt diet and has a large deficit of Na^+ in the ECF (a deficit of 2 L of ECF volume and a

deficit of 39 mmoles of Na^+ in each of the remaining 8 L of ECF (200 mmoles) because the plasma [Na^+] is 115 mM rather than the normal value of 140 mM), a positive balance of 400 to 500 mmoles of NaCl is needed. Once the ECF volume is near normal, the design of therapy reverts to contracting the ICF volume as described for Case 1 above.

– *Case 3, hyponatremia with a severe degree of hypokalemia:* A 50-kg person was placed on a low-salt diet and a thiazide diuretic for hypertension. The clinical condition of the patient has deteriorated over the past month. Several new findings are present: a poor attention span, a general lack of interest in events, profound weakness, and depression. There are no seizures or coma. On physical examination, the ECF volume appears normal (but it could be low). On laboratory examination, there is both a profound degree of hyponatremia (103 mM) and hypokalemia (1.8 mM). The EKG reveals changes consistent with hypokalemia, but there are no cardiac arrhythmias. What should the therapy be?

– *Discussion of Case 3:* The presence of this severe degree of hypokalemia has 3 major implications: a danger of a cardiac arrhythmia, a need to treat with K^+ rather than Na^+ salts, and a much greater risk of developing ODS [43]. Therefore, there are several issues here for acute therapy. One must first lessen the degree of hypokalemia to decrease the risk of developing a cardiac arrhythmia by giving oral KCl if bowel sounds are present (see Chapter I-2 on Potassium for details). Raising the plasma [K^+] to 3 mM is a reasonable initial target, but one cannot tell in advance how much K^+ will be required. If the load of KCl expands the ECF volume too much, a loop diuretic can be administered to return this volume to normal. DDAVP should be given if a large water diuresis occurs because of suppression of the release of AVP. The overall rate of correction of hyponatremia should not exceed 8 mM/day. There is also a greater danger of developing ODS in patients with hyponatremia and hypokalemia, so the rate of correction of hyponatremia should be even slower than usual (~ 5 – 6 mM/day). As in Case 2, one will need to add NaCl to the diet to repair a deficit of NaCl in the ECF.

Summary

– Do not let the plasma [Na^+] rise by more than 8 mM/day in a patient with chronic hyponatremia.
– Watch out for a water diuresis if AVP is likely to disappear.
– Do not give KCl quickly once the plasma [K^+] rises above 3.0 mM.

General Aspects about a Patient with Hypernatremia

Definition: Hypernatremia is a plasma [Na^+] > 144 mM. It is always associated with a low ICF volume; but the ECF volume may be normal, increased, or decreased.

Illustrative case: A 33–year–old woman has been on lithium for a bipolar affective disorder. While on the medication, her urine volume has increased appreciably, and she feels thirsty when she wakes up at night. She had a surgical procedure under general anesthesia early today. There were no complications in the operating room. Her perioperative intravenous fluid infusion was 3 L of isotonic saline. In the recovery room, she excreted 3 L

of urine, and her plasma [Na^+] rose to 149 mM. The urine osmolality was 107 mOsm/kg H_2O and the urine [Na^+] was 35 mM. What is the basis for her hypernatremia and how should she be treated?

Clinical Approach to the Patient with Hypernatremia

Hypernatremia indicates a negative balance for water and/or a positive balance for Na^+, although often both are responsible (Table 7). Four factors need to be assessed to determine the basis for the hypernatremia [50]. First, there will always be a disturbance of the thirst mechanism. Second, often there will be an inappropriate renal response. Third, in some cases, there will be a problem with excessive administration of Na^+, so one should evaluate the ECF volume. Fourth, one should ask about a loss of weight, since a negative balance of 1 L of EFW should cause a 1 kg weight loss.

– *Analysis of thirst:* The main defense against a reduced cell volume, as seen in hypernatremia, is to increase water intake by stimulating thirst. Because thirst is so effective, it is virtually impossible to increase the plasma [Na^+] by more than a few mM if water is available and the drinking mechanism is intact. Therefore, patients will only develop hypernatremia if they cannot appreciate thirst (e.g. patients who are unconscious or under anesthesia, as in this case example), are unable to communicate their desire for water, or if they have a decreased access to water (e.g. infants or elderly suffering from a stroke). Less frequently, hypernatremia occurs in patients with a primary defect in the thirst mechanism. Rarely, the basis for the negative water balance is reduced intake of water due to vomiting or mechanical obstruction of the upper GI tract (e.g. an esophageal tumor).

  In the above case, general anesthesia and a restricted access to water contributed to the development of hypernatremia.

– *Assessing the renal response:* The expected response to hypernatremia is the release of AVP. Therefore, urine volume should be as low as possible and the urine osmolality should be as high as possible. On a typical Western diet, one might expect a urine flow rate of approximately 0.5 ml/min and a urine osmolality > 900 mosm/kg H_2O. Failure to achieve these values indicates that an abnormal respon-

Table 7. Causes of Hypernatremia. Remember that hypernatremia is always accompanied by a reduced water intake.

A. Net primary water loss
– Reduced water intake
– Defective thirst due to altered mental state, psychological disorder, disease involving the osmoreceptor or cortical thirst center
– Inability to drink water
– Lack of water
– Increased water loss
– Renal loss: central DI, nephrogenic DI usually due to lithium or an osmotic diuresis
– Gastrointestinal loss: vomiting, osmotic diarrhea
– Cutaneous loss: sweating, fever
– Respiratory loss: hyperventilation, fever
– Water shift into the ICF
– Convulsion, rhabdomyolysis
B. Net primary Na^+ gain
– Infusion of NaCl with a higher concentration than that in the urine during polyuria
– Hypertonic NaCl or $NaHCO_3$ infusion
– Ingestion of sea water or NaCl replacing sugar in the feeding formula

DI: diabetes insipidus

se is present in most circumstances. The caveat is that one is comparing results in a patient whose osmolar excretion rate may not be the usual 600 – 900 mOsm/day.

A large loss of EFW usually occurs through the kidney (e.g. in diabetes insipidus (DI) or osmotic diuresis). Other sites of a large loss of EFW are the gastrointestinal tract (e.g. gastric suction or osmotic diarrhea) or the skin, because sweat is a hypotonic solution. Loss of water via the lungs can occur with hyperventilation, but the magnitude is not usually large.

In the above case, the low urine osmolality indicates that DI is present. The patient was given DDAVP, but there was no decrease in the urine flow rate or increase in its osmolality. Therefore, the diagnosis is nephrogenic DI, most likely due to lithium.

– *Excessive administration of Na^+:* Excessive intake of Na^+ in a normal subject does not lead to hypernatremia because the thirst mechanism is intact. Nevertheless, the basis for hypernatremia is revealed by calculating a tonicity balance (Figure 8). Excessive infusion of Na^+ can cause hypernatremia when there is an infusion of a large volume of fluid with a $[Na^+]$ higher than the urine $[Na^+]$ in a patient with polyuria due to diabetes mellitus (urine $[Na^+]$ approximately 50 mM [51]) or DI (even lower urine $[Na^+]$). Other examples include giving a large infusion of hypertonic NaCl inadvertently, the accidental entry of Na^+ into maternal circulation during abortion induced with hypertonic saline, or the administration of a large amount of hypertonic $NaHCO_3$ during cardiopulmonary resuscitation for the treatment of lactic acidosis.

In subjects who have contraction of their ECF volume and a dietary or intravenous source of Na^+, renal retention of Na^+ will contribute to hypernatremia. In fact, in patients with chronic hypernatremia due to water loss (e.g. DI), Na^+ retention may play a more important role than water loss to achieve hypernatremia.

In the above case, the tonicity balance reveals that there is an even balance for water (3 L in and 3 L out), but there is a positive balance for Na^+ of close to 300 mmoles (Figure 8). If her normal total body water is 30 L and the plasma $[Na^+]$ is normally 140 mM, then her plasma $[Na^+]$ should rise to 150 mM, close to the observed value of 149 mM. There should be a shift of 1.5 L of water from her ICF to her ECF in this case (new ECF volume = (149/140) × 10 L)). Clinically, however, this degree of ECF volume expansion may be difficult to detect on physical examination.

– *Loss of weight:* Since water is the most abundant constituent of the body, a loss of water leads to a loss of weight. Quantitatively, 1 L of water weighs 1 kg. However, weight changes are notoriously inaccurate unless the changes are large. If weight was measured in our case, there would be no loss of weight, suggesting that a gain of Na^+ was the basis for her hypernatremia. Similarly, there would be no change in weight in a patient where a shift of water into cells was the basis for the hypernatremia.

Treatment of the case patient: Hypernatremia can be treated either by the addition of water or the removal of Na^+. The choice depends on the Na^+ and water content in the patient. If depletion of water is the cause of hypernatremia, water needs to be added. If Na^+ excess is the cause, Na^+ needs to be

removed (Figure 8); this is the basis for hypernatremia in the case. We would recommend giving a loop diuretic to induce the excretion of isotonic saline and replace this volume with half-isotonic saline. Since this causes a net loss of 75 mmoles of Na^+ per L of urine, we anticipate that 4 L of exchange will be needed. Water should be given by the oral route as soon as possible.

Treatment of the Patient with Hypernatremia

– *Short-term treatment:* The principles here are to defend the ECF volume rapidly, if needed, while attending to the ICF volume more slowly. When the most important problem is a severe deficit of water, isotonic (0.9%) NaCl or 0.45% NaCl should be given initially to stabilize the "effective" circulating volume. In acute symptomatic hypernatremia, the plasma [Na^+] may be reduced by 2 mM/hour for the first 3 – 4 hours, but thereafter, the rate of decline should not exceed 1 mM/hour. As with hyponatremia, chronic hypernatremia usually does not cause central nervous system symptoms, and therefore does not require rapid correction. A safe rate of correction is a 10% fall in serum sodium over 24 hours. Avoid an excessive fall in the plasma [Na^+] because a rapid reduction of the plasma osmolality may result in brain cell swelling. The amount of water needed to correct hypernatremia can be estimated with the following equation: *Water deficit (in L) = TBW X (Target [Na^+] / Current [Na^+]).*
When the EFW deficit is mild, the oral route is the safest one. If aspiration is a concern, hypotonic fluids should be given intravenously. Give intravenous solutions that are hypotonic to the urine if polyuria is present, or hypotonic to the patient in the absence of polyuria (Figure 8). Do not give glucose if the patient is hyperglycemic. In an acutely ill patient, do not give more than 300 ml D_5W/hour, because a 70-kg patient is unlikely to metabolize glucose faster than 0.2 g/hour/kg body weight [50, 52].

– *Long-term treatment:* Disorders that require chronic preventive therapy include DI and primary hypodipsia. Although DI is often listed as a cause of hypernatremia, it should be very mild in the absence of thirst defect. Treatment is therefore directed toward the curtailment of polyuria and polydipsia which disrupt lifestyle. If hormonal deficiency is the cause of DI (central DI), DDAVP should be given either in the form of nasal spray or insufflation. In the case of nephrogenic DI, treatment should be directed towards reducing the flow to the collecting duct. This can be achieved by reducing the "effective" vascular volume with a thiazide diuretic in conjunction with decreasing the intake of salt. Loop diuretics interfere with urine concentrating mechanisms by preventing the development of a high osmolality in the medullary interstitium, through prevention of water resorption in the thin descending loop of Henle secondary to decreased Na^+ resorption in the thick ascending limb. Thus, they are not as effective as thiazide diuretics in reducing collecting duct flow.

Subjects with primary hypodipsia should be taught to drink on schedule. In some instances, the thirst center can be stimulated with chlorpropamide. When the cause of hypodipsia is a disease involving the cortical thirst center or a psychological disorder, a slight increase in water intake will restore

water balance, and hence prevent hypernatremia. When hypodipsia is caused by destruction of the osmoreceptor, increased water intake will be followed by a marked increase in urine output long before the correction of hypernatremia. As the effective circulating volume is expanded by an increase in water intake, the ECF volume depletion-mediated stimulation of AVP wanes. This in turn leads to unmasking of DI, accompanied by polyuria and polydipsia. These patients will therefore have to be treated with DDAVP, as well as the intake of a set amount of water.

Measurement of body weight at regular intervals can detect net water loss leading to hypernatremia. A clinically significant increase in the plasma [Na^+] will be accompanied by a substantial weight loss. For example, if a person with a total body water of 40 L were to increase his plasma [Na^+] from 140 mM to 155 mM by pure water loss, the amount of water loss would have to be close to 4 L, or a weight loss of 4 kg.

Weight changes can also be used to guide the curtailment of water intake in those treated with exogenous AVP. If AVP action is continuously maintained by exogenous AVP administration, these patients have a form of SIADH. Unregulated intake of water can lead to hyponatremia. Daily monitoring of weight will allow one to suspect excessive water retention without measuring the plasma [Na^+]. A substantial weight gain will be accompanied by a significant reduction in the plasma [Na^+]. Another approach one can take to prevent the development of hyponatremia in patients treated with exogenous AVP is to allow the patients to develop a diuresis every few days until the patient experiences thirst. Thirst is experienced when the plasma [Na^+] rises slightly above its usual normal level. This approach of course would not be feasible in those with a disease process involving the thirst center.

Summary

- *Danger:* Hypernatremia means ICF volume contraction; the main danger is an intracerebral hemorrhage due to a reduction in ICP.
- *Diagnosis:* Four questions dominate the clinical picture:
  1. Why is there a problem with thirst?
  2. Is the renal response appropriate?
  3. Is the ECF volume contracted?
  4.Was there a loss of weight (quantitatively reflecting the negative balance for EFW)?
- *Therapy:* Reexpand the ICF volume slowly (fall in serum sodium of close to 10% per day unless hypernatremia is very acute). Maintain a normal ECF volume.
- *Caution:* There is a danger of a glucose load in a patient who needs a large, intravenous input of EFW (as D_5W). In general, do not give more than 300 ml D_5W/hr and do not give D_5W if hyperglycemia is present.

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