

2

The patient with fluid, electrolyte, and divalent ion disorders

- 2.1 Hypo–hypernatraemia: disorders of water balance 213
Nicolaos E. Madias and Horacio J. Adrogé
- 2.2 Hypo–hyperkalaemia 241
Richard L. Tannen and Kenneth R. Hallows
- 2.3 Hypo–hypercalcaemia 269
Neveen A.T. Hamdy and John A. Kanis
- 2.4 Hypo–hyperphosphataemia 287
Caroline Silve and Gérard Friedlander
- 2.5 Hypo–hypermagnesaemia 309
John H. Dirks
- 2.6 Clinical acid–base disorders 321
Biff F. Palmer, Robert G. Narins, and Jerry Yee

2.1 Hypo–hypernatraemia: disorders of water balance

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Disturbances in the serum sodium concentration, known as hyponatraemia and hypernatraemia, are the most common electrolyte disorders encountered in clinical practice. The resultant morbidity varies widely: hyponatraemia and hypernatraemia can be largely inconsequential but at times they can claim the patient's life. Although diagnosis and management can be straightforward, quite often they prove challenging even to experienced physicians. The complexity underlying these disorders is highlighted by the fact that dysnatraemias are frequently hospital-acquired—essentially iatrogenic. Further, some of their most dreaded consequences result not from the disorders themselves, but rather from inappropriate management. Optimal treatment of abnormalities in serum sodium concentration demands considerable pathophysiological insight, sound clinical judgement, and, when the dysnatraemia is severe, frequent monitoring of the patient's clinical status and laboratory parameters.

Serum tonicity and, thus, serum sodium concentration are tightly adjusted by the normally exquisite regulation of water homeostasis. Water intake and renal water excretion are adjusted through the control of thirst and the release of vasopressin (antidiuretic hormone, ADH). Therefore, hyponatraemia and hypernatraemia primarily reflect disruptions of water homeostasis. In this chapter, we first review principles of water homeostasis and then summarize the pathophysiological and clinical aspects of hyponatraemia and hypernatraemia.

Principles of water homeostasis

Body fluid tonicity and osmolality

Tonicity defines the forces that determine the net flux of water between two solutions separated by a membrane permeable to water but impermeable to certain solutes contained in the solutions. In such a system, water flows from the more dilute to the more concentrated solution (as defined by the concentration of those solutes that are constrained in their movement across the cell membrane). Osmolality, a physical property of solutions, refers to the forces generated by solutes that reduce the random movement of water molecules; such forces depend only on the concentration, not the nature, of all particles in the solution. Because some of the solutes that are regularly or frequently present in body fluids, most notably urea and ethanol, permeate cell membranes as freely as water, these solutes contribute to osmolality but have no impact on tonicity. This distinction is made by the term effective osmolality that is synonymous to tonicity.

Serum osmolality can be thoroughly assessed by three closely related variables: measured osmolality, calculated osmolality, and tonicity or

effective osmolality. Serum osmolality, a property dependent on total solute concentration (i.e. all particles in solution), is measured with an osmometer. This instrument evaluates changes in other physical properties of particles in solution, such as the freezing point or the water vapour pressure of the solution, which are then 'translated' into osmolality. The value obtained, the measured serum osmolality, fails to differentiate between total solute and those solutes that translocate water from one compartment to another across cell membranes.

Calculated serum osmolality is obtained from the measured concentrations of sodium, glucose, and urea, the three major low-molecular-weight solutes contained in serum, as follows:

$$\begin{aligned} \text{Serum osmolality, mOsm/kg H}_2\text{O} \\ &= [\text{Na}^+, \text{mmol/l}] \times 2 + [\text{glucose, mg/dl}]/18 \\ &\quad + [\text{BUN, mg/dl}]/2.8 \end{aligned} \quad (1)$$

where BUN refers to blood urea nitrogen, a commonly measured substitute of urea itself. The multiplier 2 overestimates the osmotic force created by sodium and its accompanying anions, as the activity (dissociation factor) of the sodium salts is approximately 1.86 in extracellular fluid (ECF) (due to ion interactions in a relatively concentrated solution). The dissociation factor would be precisely 2 in ideal solutions with maximal dilution and absence of substantial ion interactions. However, using 2 instead of 1.86 in Eq. (1) compensates for the osmotic contribution of other low-molecular-weight serum constituents (i.e. potassium, calcium, and magnesium and their accompanying anions) present at low concentrations. The concentration of glucose and urea (non-ionic solutes) expressed in mmol/l corresponds to their contribution to osmolality in mOsm/kg H₂O. When reported in mg/dl, a usual practice in many countries, glucose must be divided by 18 (molecular weight of glucose is 180) and BUN by 2.8 (28 being the contribution of nitrogen to the molecular weight of urea, which is 60) to convert mg/dl to mmol/l. On account of their large molecular weight, serum proteins make a meagre contribution to serum osmolality that is essentially ignored. Taking the average normal values for the three solutes included in Eq. (1), that is, 140 mmol/l for sodium, 90 mg/dl for glucose, and 15 mg/dl for BUN, one can derive a calculated osmolality of 290 mOsm/kg H₂O, a value virtually identical to the average normal serum osmolality measured with an osmometer. Barring laboratory error, the finding of an 'osmolar gap', defined as measured serum osmolality exceeding calculated serum osmolality by at least 10 mOsm/kg H₂O, must reflect either the presence in serum of additional low-molecular-weight solute(s) at substantial concentration(s) (e.g. ethanol, methanol, ethylene glycol, mannitol) or a substantial decrease in serum water content coupled with measurement of serum sodium concentration by flame photometry or

an indirect electrode technique involving dilution of the sample (i.e. pseudohyponatraemia).

Serum tonicity or effective osmolality is calculated by adding the osmolar contribution of sodium and its accompanying anions to that of glucose, as follows:

$$\begin{aligned} \text{Serum tonicity (effective osmolality), mOsm/kg H}_2\text{O} \\ = [\text{Na}^+, \text{mmol/l}] \times 2 + [\text{glucose, mg/dl}]/18 \end{aligned} \quad (2)$$

Mannitol, an additional, albeit uncommon, solute that is compartmentalized in the ECF, contributes to serum effective osmolality. In contrast, urea crosses cell membranes freely, and, therefore, makes no contribution to serum effective osmolality. The normal range for effective osmolality is 275–290 mOsm/kg H₂O with an average value of 285 mOsm/kg H₂O. Corresponding values for serum osmolality are 280–295 mOsm/kg H₂O (normal range) with an average value of 290 mOsm/kg H₂O.

Water balance

Maintenance of water balance (homeostasis) requires identical levels of water intake and water losses. The daily obligatory (i.e. minimal) extrarenal water loss amounts to approximately 500 ml of water—the difference between water losses from the skin and lungs (dubbed insensible losses) of about 1000 ml and water production by oxidative metabolism of about 500 ml. A small amount of water is lost in the stool. In turn, the daily obligatory renal water loss depends on urinary solute excretion. Increases in solute excretion reduce the maximal urine osmolality, that is, that achieved in the presence of maximal levels of ADH, thereby increasing the daily obligatory renal water loss (Fig. 1). Daily ingestion of 70 g of protein and 10 g of sodium chloride, a usual diet in many countries, generates approximately 700 mOsm of solute that must be excreted by the kidney to strike daily solute balance. Considering a maximal urine concentration during antidiuresis of approximately 900 mOsm/kg H₂O when urine solute excretion is at 700 mOsm/day, the obligatory daily urine volume would be of the order of 800 ml. For this level of solute load, a minimum of 1300 ml (i.e. 800 + 500) of water must be ingested daily to replace the renal

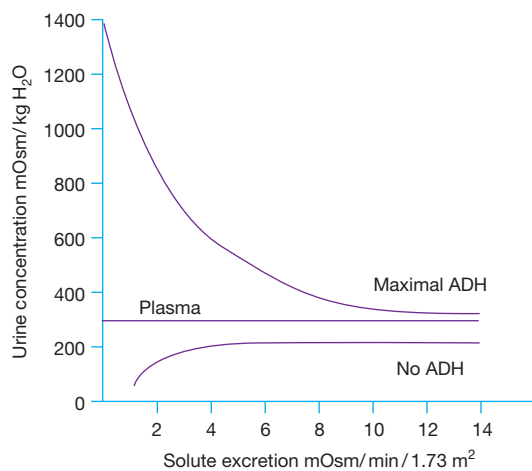


Fig. 1 Effect of solute excretion on maximal and minimal urine osmolality [maximal level of antidiuretic hormone (ADH) or absence of ADH, respectively]. [Modified from de Wardener H.E. and del Greco F. (1955). *Clinical Science* **14**, 715.]

and extrarenal (insensible) fluid losses. Water homeostasis and body fluid tonicity would then remain normal. However, water intake can be substantially larger than the minimal amount; in such a case, a corresponding increase in renal fluid loss ensures water balance and normal body fluid tonicity. Taken to the extreme, at a maximal urine dilution of about 50 mOsm/kg H₂O, daily excretion of 14 l of urine can be attained for the same level of solute excretion (700/50) thereby accommodating up to 14.5 l of water intake (balancing renal and extrarenal losses) without risking a decrease in body fluid tonicity.

The typical water intake of humans exceeds the minimum requirement for maintaining water balance and is largely determined by social and cultural influences. Thus, normal adults usually ingest approximately 1.5–2.5 l of water per day; the corresponding urine volume is of the order of 1–2 l per day assuming the usual, low rate of insensible losses. However, when exercise, hot weather, or high fever stimulates sweating and pulmonary ventilation, extrarenal water losses increase markedly, occasionally exceeding 5 l/day. The ensuing increase in serum tonicity stimulates thirst and vasopressin release; in turn, increase in water intake coupled with renal water conservation restores water balance and normal serum tonicity.

Role of thirst

Thirst plays a critical role in water balance as demonstrated by the fact that sustained hypertonicity and hypernatraemia occur only when thirst or access to water is impaired. Hypertonicity is the most potent stimulus for thirst. The level at which the sensation of thirst arises, the tonicity threshold for thirst, is reached with a 2–3 per cent increase in serum tonicity (i.e. to an average level of 290 mOsm/kg H₂O), a value that is normally about 5 mOsm/kg H₂O higher than that which stimulates vasopressin release. Some investigators, however, have reported similar tonicity thresholds for thirst and vasopressin release (Thompson *et al.* 1991). The tonicity sensors are neurons residing in the anterior hypothalamus close to the supraoptic nuclei. The same sensors might control both thirst and vasopressin release, but the existence of two different sensors has not been excluded. Activation or inhibition of these sensing cells appears to result from changes in cell volume triggered by tonicity-induced water shifts.

The ECF volume provides an additional control mechanism of thirst mediated by low-pressure baroreceptors located in the cardiac atria, whose discharge is transmitted to the brain via the vagus nerve. Hypovolaemia also stimulates the renin–angiotensin system, angiotensin II reaching the hypothalamus where it exerts a potent dipsogenic effect (Mann *et al.* 1987). Other factors also affect thirst, including a dry mouth and social influences.

Several factors mediate cessation of thirst or water satiety, such as the central tonicity sensors, oropharyngeal mechanoreceptors stimulated by swallowing large volumes of fluid, and distension of the stomach.

Role of vasopressin and the kidney

Arginine vasopressin, the human form of ADH, is a nine-amino acid peptide consisting of a six-amino acid ring with a three-amino acid side chain. Vasopressin is synthesized as a large prohormone in the cells of the supraoptic and paraventricular nuclei of the hypothalamus and transported in secretory granules to the neural lobe (neurohypophysis or posterior pituitary). In the secretory granule, the prohormone is cleaved and enzymatically processed into vasopressin, neurophysin, and the vasopressin-binding glycopeptide. Vasopressin

is stored in secretory granules within the nerve terminals in the neurohypophysis, bound to its neurophysin. Depolarization of the nerve terminals, caused by activation of cation channels, releases the bound peptides, vasopressin and neurophysin, into the circulation, where vasopressin dissociates from the other peptide, becoming an active hormone (Oliet and Bourque 1993). Vasopressin is degraded in the liver and kidney, its half-life in the circulation being only 15–20 min.

Control of vasopressin secretion

ADH secretion is stimulated by hypertonicity and decreased ECF volume or arterial blood pressure (Fig. 2) (Robertson 1987). Released vasopressin leads to water retention by the kidney that in turn corrects hypertonicity and normalizes ECF volume and blood pressure. Conversely, hypotonicity decreases ADH release promoting water diuresis, negative fluid balance, and restoration of normal tonicity. A large water load lowers serum tonicity, shuts off ADH release and promotes excretion of more than 80 per cent of the ingested water within 4 h; about 90–120 min elapse before maximal diuresis appears, an interval required for absorption of water and degradation of circulating ADH. Volume expansion, on the other hand, has little effect on vasopressin release.

Tonicity

Only effective osmoles trigger vasopressin release. Thus, administration of hypertonic saline or mannitol increases serum tonicity, which in turn promotes water exit from the tonicity sensing cells; the resulting decrease in osmoreceptor cell volume elicits their activation. Conversely, urea, an ineffective osmole, crosses cell membranes freely and therefore fails to change serum tonicity or cell volume. At a serum tonicity less than 280 mOsm/kg H₂O, circulating vasopressin is undetectable under normal conditions (Fig. 2). The osmoreceptor cells are sensitive to changes in serum tonicity as small as 1 per cent, this exquisite response fostering the remarkable stability of serum tonicity. In fact, despite wide variations in water intake, serum tonicity normally does not fluctuate by more than 1–2 per cent. The tonicity threshold for ADH secretion ranges from 280 to 290 mOsm/kg H₂O,

a variation due, in part, to the modulating influence of changes in ECF volume and blood pressure. At a tonicity of about 290 mOsm/kg H₂O the released vasopressin reaches serum levels that cause maximal antidiuresis in normal subjects. However, vasopressin levels progressively increase at higher levels of serum tonicity (Fig. 2).

Because serum sodium and its accompanying anions largely determine ECF tonicity (Eq. 2), serum sodium concentration is essentially the primary stimulus to vasopressin release. Glucose, the other potentially major extracellular solute, behaves as an effective osmole promoting ADH release only in states of insulin deficiency, such as uncontrolled diabetes mellitus (DM). In normal subjects, however, the hyperglycaemia-induced insulin release promotes glucose entry into the osmoreceptor cells thereby rendering glucose an ineffective osmole.

ECF volume and blood pressure

The discharge rate from parasympathetic afferent nerves in the carotid sinus baroreceptors modifies vasomotor-centre activity in the medulla and, in turn, release of vasopressin produced in the paraventricular nuclei (Abramow *et al.* 1987). In contrast, the supraoptic nuclei participate only in tonicity-induced changes in ADH secretion. Thus, increased discharge from these afferent nerves in states of decreased effective circulating volume (e.g. vomiting, cirrhosis, heart failure) increases vasopressin release. Low-pressure receptors located in the left atrium have no significant role in ADH secretion in humans (only in the control of thirst) unless systemic blood pressure has also decreased (Bie *et al.* 1986). A 10 per cent reduction in ECF volume is required to stimulate ADH release; greater degrees of hypovolaemia cause an exponential increase in plasma vasopressin, yielding concentrations that far exceed those attained in response to hypertonicity (Fig. 2) (Baylis 1987). Blood pressure reductions lower than 10 mm Hg have little effect on vasopressin secretion, but more severe hypotension is a potent stimulus to ADH release.

Whereas hypovolaemia, a nonosmotic stimulus to ADH release, potentiates the ADH response to hypertonicity, it can also override the inhibitory effect on ADH secretion normally exerted by hypotonicity (Fig. 2). The latter concept finds important clinical application in the hyponatraemias associated with states of decreased effective circulating volume.

Other factors

Additional factors or conditions alter ADH secretion, most notably nausea, pain, surgery, pregnancy, and several drugs. Nausea is probably the strongest known stimulus to ADH release, as it can increase vasopressin up to 500-fold by mechanisms that remain undetermined. Pain, especially following surgery, triggers ADH release, which, together with a large intake of water or hypotonic fluids, promotes water retention and dilutional hyponatraemia.

Pregnancy is associated with a decrease in serum sodium of about 5 mmol/l because of a downward resetting of the osmoregulatory threshold for both vasopressin release and thirst (Lindheimer *et al.* 1989). Multiple factors, conditions, and drugs listed in Table 1 stimulate or inhibit vasopressin release; compounds are also listed that potentiate the renal effects of ADH or cause water retention by undefined mechanisms.

Effects of vasopressin

Vasopressin acts through its interaction with three types of receptors coupled to G proteins (Bichet *et al.* 1988; Sugimoto *et al.* 1994). The V1a receptor mediates pressor and proliferative effects in vascular

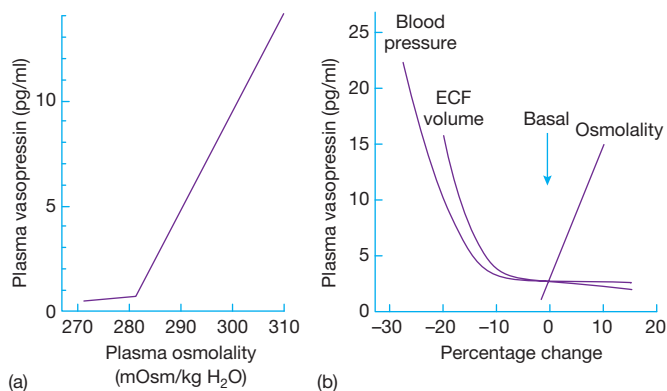


Fig. 2 Relationship between plasma vasopressin and osmolality (a) and plasma vasopressin and percentage change in blood pressure, ECF volume, and osmolality (b). A 5 per cent increase in serum osmolality is sufficient to change plasma vasopressin from undetectable levels to levels effecting maximal urine concentration. On the other hand, ECF volume or blood pressure must be reduced by 10–15 per cent to trigger vasopressin release. (Modified from Gennari 1998; Robertson 1992.)

Table 1 Factors, conditions, and drugs that alter renal water excretion by changing the level or renal action of vasopressin (ADH)

Stimulation of ADH release	Inhibition of ADH release	Drugs that potentiate renal action of ADH	Drugs that cause water retention by unknown mechanism
Hypertonicity	Hypotonicity	Chlorpropamide	Haloperidol
Volume contraction	Volume expansion	Cyclophosphamide	Fluphenazine
Hypotension	Hypertension	Non-steroidal	Amitriptyline
Nausea/emesis	Hormones/drugs	anti-inflammatory	Thioridazine
Hypoglycaemia	Opioids (κ and agonists)	drugs	Fluoxetine
Severe heart failure	Sympathetic	Acetaminophen	Sertraline
Severe liver failure	amines (β agonists)		Ecstasy
Hypothyroidism	Ethanol		
Adrenal insufficiency			
Hormones/drugs			
Angiotensin II			
Sympathetic amines			
(α 1 agonists)			
Histamine			
Bradykinin			
Opioids (μ agonists)			
Nicotine			
Antipsychotics/			
antidepressants			
Ifofamide			
Chlorpropamide			
Carbamazepine			
Narcotics			
Vincristine			
Clofibrate			

smooth muscle cells as well as stimulation of coagulation through the release of procoagulant factors (factor VIII and von Willebrand's factor) from vascular endothelium and increased platelet aggregation. The V1b receptor, limited to anterior pituitary cells, facilitates the release of adrenocorticotrophic hormone (ACTH). The V2 receptor, present in the basolateral membrane of the principal cells of cortical and medullary collecting tubules, mediates the ADH-induced stimulation of water permeability thereby permitting osmotic equilibration with the renal interstitium (Fig. 3) (Agre 2000). Vasopressin interaction with this receptor activates adenylate cyclase and generates the second messenger, cyclic AMP, which then initiates a sequence of events that leads to the exocytotic insertion of cytosolic water channels (aquaporin-2) into the apical membrane of the principal cells of the collecting tubule (Fig. 3) (Deen *et al.* 1994; Sasaki *et al.* 1994). These water channels permit water movement into the cells down a favourable osmotic gradient; water then rapidly exits across the basolateral membrane (via the constitutive water channel, aquaporin-3) to the systemic circulation. When the vasopressin effect dissipates, the water channels are removed from the apical membrane by endocytosis and returned to the cytoplasm (Harris *et al.* 1991). Vasopressin also stimulates the renal production of prostaglandin E_2 and prostacyclin within several renal structures, including the glomerular mesangium, thick ascending limb, collecting tubules, and medullary interstitium (Bonvalet *et al.* 1987). These prostaglandins reduce both the antidiuretic and vascular actions of ADH, thereby preventing an excessive antidiuretic response and possibly maintaining renal perfusion (Yared *et al.* 1985; Hebert *et al.* 1990). Further, vasopressin stimulates sodium reabsorption in the thick ascending limb of the loop of Henle in some species, but it is unclear whether this action occurs in humans.

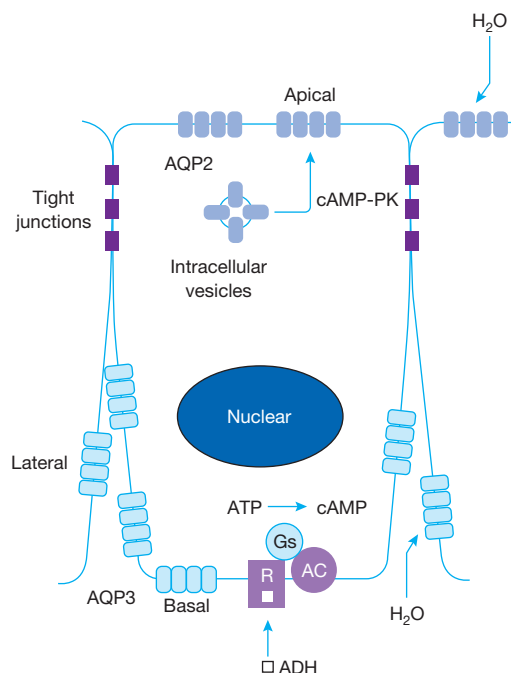


Fig. 3 Diagram of vasopressin effects on the collecting duct principal cell indicating water channel (aquaporin-2, AQP2) insertion in the apical membrane. The basolateral membrane contains a different constitutive water channel (aquaporin-3, AQP3). (Modified from Agre 2000.)

The kidney and water excretion

Regulation of water balance largely rests with the kidney's ability to excrete urine with an osmolality that varies from a minimum of 50 mOsm/kg H₂O to a maximum of 900–1400 mOsm/kg H₂O (Fig. 1). This wide range of urine osmolality reflects adjustments in collecting duct water permeability from a low value in the absence of vasopressin (production of dilute urine, water diuresis) to a high value in the presence of vasopressin (production of concentrated urine, antidiuresis).

The ability of the kidney to produce maximal urine dilution in states of water excess depends on three crucial steps, including: (a) adequate delivery of filtered fluid to the collecting tubule thereby ensuring sufficiently high flow rates that prevent the equilibration of collecting duct urine with the hypertonic renal interstitium; at low flow rates, osmotic equilibration can occur even in the absence of vasopressin thereby producing concentrated urine; adequacy of distal delivery requires a normal glomerular filtration rate and normal (not increased) proximal fluid reabsorption; (b) active sodium chloride transport without water in the thick ascending limb of the loop of Henle (impermeable to water), which reduces the osmolality of fluid entering the distal tubule to 50–100 mOsm/kg H₂O; and (c) absence of vasopressin, thereby maintaining the intrinsically low water permeability of the collecting duct.

On the other hand, the capacity of the kidney to produce maximal urine concentration and thus minimize water loss in states of water depletion requires the following critical steps: (a) active sodium chloride transport without water in the thick ascending limb of the loop of Henle (impermeable to water) thereby producing dilution of the tubular fluid and concentration of the renal interstitium; (b) enhancement of the effect of step (a) by the entry of sodium chloride into the descending limb of the loop of Henle (hairpin configuration) and the exit of water from this segment (through water channels known as aquaporin-1) thereby raising progressively the osmolality both of the luminal fluid of the descending limb of the loop of Henle and the renal interstitium from the corticomedullary junction to the inner medulla (Chou *et al.* 1999); this process is known as countercurrent multiplication mechanism (Sands and Kokko 1996); (c) maintenance of the corticomedullary osmotic gradient by the vasa recta (hairpin configuration similar to that of the loops of Henle and in direct juxtaposition with them) that reach osmotic equilibrium with the interstitium, as they are permeable to solutes and water and remove fluid from the renal interstitium (ascending vasa recta blood flow is almost twice that of descending vasa recta) (Zimmerhackl *et al.* 1985); this process is known as countercurrent exchange mechanism; (d) preservation of a relatively low medullary and papillary blood flow that prevents the removal of solutes (largely sodium chloride and urea) from the renal interstitium; and (e) presence of vasopressin to ensure high water permeability of the collecting duct.

Measurement of urine osmolality (or its imperfect substitute, urine specific gravity) is usually sufficient to assess the renal response to water excess or deprivation. An additional tool introduced for the same purpose, free water clearance, is conceptually cumbersome and lacks practical utility. Free water clearance represents the difference between measured urine volume (per unit time) and the calculated volume required to excrete the solute contained in that urine at a concentration isotonic to serum. A urine more dilute than serum, expected in water excess, exceeds the volume of the calculated isotonic urine, the volume difference being termed positive free water clearance. A urine more concentrated than serum, expected in water depletion, falls short of the

volume of the calculated isotonic urine, the volume difference being termed negative free water clearance. The latter term is particularly confusing as there is no gain of water by the kidney in the presence of negative free water clearance, but only a reduction of the water loss required to accommodate the obligatory solute load. In short, the clinical evaluation and management of disorders of water balance do not require assessment of this parameter.

Clinical disorders of water homeostasis

The disorders of sodium and water homeostasis can be classified into three major categories: (a) abnormalities in the size of ECF volume; (b) disturbances in the tonicity of body fluids; and (c) selective deficit or excess of sodium or chloride.

The first group of disorders comprises an enlargement (volume excess or expansion) or a reduction (volume depletion or contraction) in the ECF volume due to a combined and proportional sodium and water excess or deficit, respectively. Disorders of sodium balance are the primary causes of ECF volume excess or depletion. Sodium chloride excess only transiently increases tonicity; the resulting stimulation of thirst and ADH secretion causes water retention, and prevents sustained hypernatraemia. Expansion of ECF volume is the hallmark of this disorder. In an analogous fashion, sodium chloride deficit only transiently decreases tonicity; inhibition of ADH secretion with secondary increase in water excretion prevents sustained hyponatraemia. Depletion of ECF volume is the chief manifestation of this disturbance.

Sustained disturbances in the tonicity of body fluids include increases or decreases in the effective osmolality of body fluids manifested as hypernatraemia or hyponatraemia (hypotonic), respectively. A disproportion between sodium and water content of body fluids underlies hypernatraemia (water content is relatively small for the concomitant sodium content) and hyponatraemia (water content is relatively large for the concomitant sodium content). As hypernatraemia and hyponatraemia are concentration terms, either entity can occur in association with a decreased, normal, or increased sodium content. A primary and isolated disturbance in water balance, deficit or excess, causes hypertonicity (hypernatraemia) or hypotonicity (hyponatraemia), respectively, but does not substantially alter the size of the ECF compartment—the size of this compartment is primarily determined by its sodium content, a variable unaltered in exclusive disturbances of water balance.

A comparison of volume regulation (altered in disorders of sodium balance) and osmoregulation (altered in disorders of water balance) further clarifies important differences between sodium and water homeostasis and their disorders. Whereas effective circulating volume is sensed by receptors in the carotid sinus, atria, and afferent glomerular arteriole in volume regulation, it is serum tonicity that is sensed by hypothalamic osmoreceptors in osmoregulation. Volume regulation is achieved by the control of renal sodium excretion that is mediated by multiple mechanisms, including the sympathetic nervous system, renin–angiotensin–aldosterone, natriuretic peptides, and pressure natriuresis. On the other hand, osmoregulation is accomplished by the control of water balance that is mediated by thirst/water satiety and modulation of renal water excretion via changes in ADH secretion.

In contrast to the first two groups of sodium and water disorders, the third group is characterized by an abnormal relationship between the serum sodium and chloride concentrations. Whereas the serum sodium

concentration is generally maintained within the normal limits in these disorders (unless there is an accompanying abnormality of water homeostasis), the serum chloride concentration is either abnormally high or low. The hyperchloraemic type of this form of $[\text{Na}^+]/[\text{Cl}^-]$ imbalance comprises hyperchloraemic metabolic acidosis and chronic respiratory alkalosis, whereas metabolic alkalosis and chronic respiratory acidosis represent the hypochloraemic type of this imbalance. Importantly, the three major categories of disorders of sodium and water balance described above can coexist in a single patient.

Determinants and measurement of serum sodium concentration

Under normal conditions, the serum sodium concentration is an accurate indicator of serum tonicity because sodium and its anions account for virtually all the effective osmoles present in the ECF (Eq. 2). Thus, it can be assumed that

$$\text{Serum tonicity} \cong 2 \times \text{serum } [\text{Na}^+] \quad (3)$$

Because the hydraulic permeability of most cell membranes is very high, water moves freely and rapidly between the ECF and intracellular fluid (ICF) establishing an identical tonicity in the two compartments. In contrast with the ECF, potassium is the major solute responsible for the tonicity of the ICF. Consequently, a predictable relationship exists between serum tonicity on the one hand, and total body 'exchangeable' (i.e. osmotically active) sodium and potassium content (Na_E^+ and K_E^+ , respectively) and total body water, on the other, which can be expressed as follows:

$$\text{Serum tonicity} = \frac{2 \times \text{Na}_E^+ + 2 \times \text{K}_E^+}{\text{Total body water}} \quad (4)$$

where the multiplier 2 accounts for the accompanying anions. Note that the Na_E^+ and K_E^+ determine the size of the ECF and ICF compartment, respectively. Combining Eqs (3) and (4) one can derive Eq. (5), which states that the serum sodium concentration is determined by the ratio of the 'exchangeable' portions of the body's sodium and potassium content to total body water:

$$\text{Serum } [\text{Na}^+] \cong \frac{\text{Na}_E^+ + \text{K}_E^+}{\text{Total body water}} \quad (5)$$

The fundamental relationship embodied in Eq. (5) offers clear insight into a number of clinically important principles: (a) The level of serum sodium is a concentration term that is fixed by the body's 'exchangeable' sodium and potassium content relative to the prevailing total body water. Changes in these variables represent the limited ways through which alterations in serum sodium concentration can occur. (b) Being a concentration term, serum sodium offers no insights into the status of the body's sodium stores; hypernatraemia and hyponatraemia can each occur in the presence of contracted, normal, or expanded sodium stores. Thus, hypernatraemia and hyponatraemia should primarily be viewed as disturbances in water, rather than sodium, balance. (c) Correction of an abnormality in serum sodium concentration entails manipulation of the intake of sodium, potassium, and water relative to their output.

Serum sodium concentration, classically measured by flame photometry, ranges normally from 136 to 145 mmol/l, with an average value of 140 mmol/l. Because water normally comprises 93 per cent of

the serum volume, and sodium is restricted to serum water, the average $[\text{Na}^+]$ in serum water is approximately 150 mmol/l ($140/0.93 = 150$). However, measurement of serum $[\text{Na}^+]$ by flame photometry has gradually been displaced by the use of the sodium ion-specific electrode, which senses the Na^+ activity in the aqueous phase of serum. At the normal ionic strength of serum water, Na^+ activity is approximately 75 per cent that of $[\text{Na}^+]$; because the normal value of $[\text{Na}^+]$ in serum water is approximately 150 mmol/l, the normal value of $[\text{Na}^+]$ activity is 150×0.75 or 112 mmol/l (Maas *et al.* 1985). To avoid major confusion due to the introduction of a new range of normal values, an empirical correction factor is used in the clinical laboratory such that the normal range of $[\text{Na}^+]$ remains the same as if the sample were measured by flame photometry. Measurement of serum $[\text{Na}^+]$ by means of an ion-specific electrode has now been widely adopted by most clinical laboratories as part of an automated system that performs multiple analysis.

Direct measurement of $[\text{Na}^+]$ by the ion-specific electrode has eliminated pseudohyponatraemia. A spurious form of iso-osmolar and isotonic hyponatraemia, pseudohyponatraemia is identified when severe hypertriglyceridaemia or paraproteinaemia increases substantially the solid phase of serum (i.e. decreases the fraction of water in serum volume) and the sodium concentration is measured by means of flame photometry or by an electrode technique involving dilution of the sample. In contrast, the activity of Na^+ measured in an undiluted sample is unaffected by changes in serum water content, and it is automatically corrected by the ion-specific electrode to a concentration based on normal serum water content.

Hyponatraemia

Hyponatraemia is defined as a serum sodium concentration less than 136 mmol/l. Whereas hypernatraemia always denotes hypertonicity, hyponatraemia can be associated with low, normal, or high tonicity.

Dilutional hyponatraemia, by far the most common form of the disorder, is caused by water retention. If water intake exceeds the capacity of the kidney to excrete water, dilution of body solutes ensues with hypo-osmolality and hypotonicity (Fig. 4b, e, f, and g). Hypotonicity, in turn, can lead to cerebral oedema, a potentially life-threatening complication. Hypotonic hyponatraemia can be associated, however, with normal or even high serum osmolality if sufficient amounts of solutes that permeate cell membranes (e.g. urea and ethanol) have been retained (Fig. 4c). Importantly, patients who have hypotonic hyponatraemia but normal or high serum osmolality are as subject to the risks of hypotonicity as are patients with hypo-osmolar hyponatraemia.

Non-hypotonic hyponatraemia

The non-hypotonic hyponatraemias include hypertonic (or translocational) hyponatraemia, isotonic hyponatraemia, and pseudohyponatraemia. Translocational hyponatraemia results from a shift of water from cells to the ECF that is driven by solutes confined in the extracellular compartment (as occurs with hyperglycaemia in uncontrolled DM or retention of hypertonic mannitol); serum osmolality is increased, as is tonicity, the latter causing dehydration of cells (Fig. 4d). Hyperglycaemia is the most common cause of translocational hyponatraemia. An increase of 100 mg/dl (5.6 mmol/l) in the serum glucose concentration decreases serum sodium by approximately 1.6 mmol/l, the end result being a rise in serum osmolality of approximately 2.0 mOsm/kg H_2O .

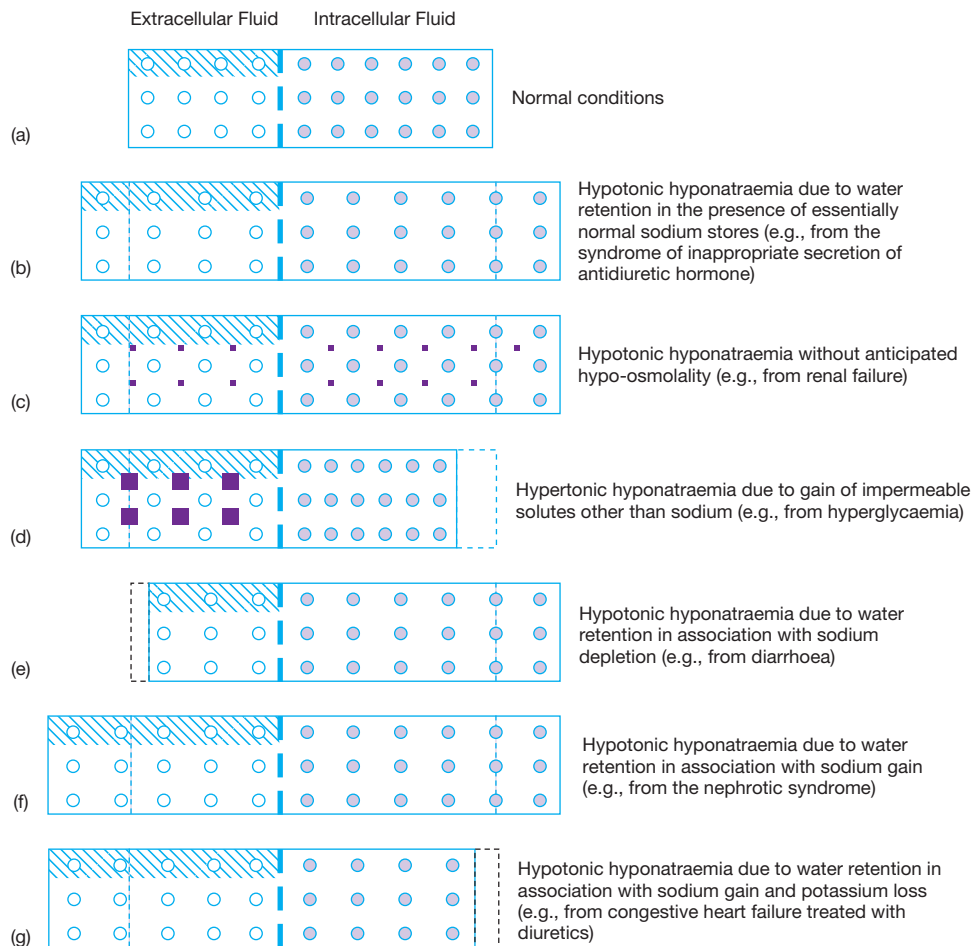


Fig. 4 Extracellular-fluid and intracellular-fluid compartments under normal conditions and during states of hyponatraemia. Normally, the ECF and ICF compartments make up 40 and 60 per cent of total body water, respectively (Panel a). With the syndrome of inappropriate secretion of antidiuretic hormone, the volumes of ECF and ICF expand (although a small element of sodium and potassium loss, not shown, occurs during inception of the syndrome) (Panel b). Water retention can lead to hypotonic hyponatraemia without the anticipated hypo-osmolality in patients who have accumulated ineffective osmoles, such as urea (Panel c). A shift of water from the ICF compartment to the ECF compartment, driven by solutes confined in the ECF, results in hypertonic (translocational) hyponatraemia (Panel d). Sodium depletion (and secondary water retention) usually contracts the volume of ECF but expands the ICF compartment. At times, water retention can be sufficient to restore the volume of ECF to normal or even above-normal levels (Panel e). Hypotonic hyponatraemia in sodium-retentive states involves expansion of both compartments, but predominantly the ECF compartment (Panel f). Gain of sodium and loss of potassium in association with a defect of water excretion, as they occur in congestive heart failure treated with diuretics, lead to expansion of the ECF compartment but contraction of the ICF compartment (Panel g). In each panel, open circles denote sodium, solid circles potassium, large squares impermeable solutes other than sodium, and small squares permeable solutes; the broken line between the two compartments represents the cell membrane, and the shading indicates the intravascular volume.

Hypertonic mannitol, retained in patients with renal insufficiency, has the same effect. In both conditions, the resultant hypertonicity can be aggravated by osmotic diuresis; mitigation of hyponatraemia or frank hypernatraemia can develop, as the total of the sodium and potassium concentrations in the urine falls short of that in serum. Retention in the extracellular space of large volumes of isotonic fluids that do not contain sodium (e.g. isotonic mannitol solution) generates iso-osmolar and isotonic hyponatraemia but no transcellular shifts of water. Massive absorption of isotonic irrigant solutions that are sodium free (e.g. those used during transurethral prostatectomy or for control of uterine bleeding) can cause severe hyponatraemia. Pseudohyponatraemia, as described above, is a spurious form of iso-osmolar and isotonic hyponatraemia that represents a laboratory artefact. Direct measurement of

serum sodium with the ion-specific electrode in undiluted sample eliminates this artefact.

Hypotonic hyponatraemia

Hypotonic (dilutional) hyponatraemia is a common clinical problem in hospitalized patients. Although morbidity varies widely in severity, serious complications can arise from the disorder itself as well as from errors in management. Hypotonic hyponatraemia represents an excess of water in relation to existing sodium stores, which can be decreased, essentially normal, or increased (Fig. 4). Retention of water most commonly reflects ingestion of a usual amount of water on the background of impaired renal water excretion; in a minority of cases, it is

caused by excessive water intake, with a normal or nearly normal water excretory capacity (Table 2).

Impaired capacity of renal water excretion

Clinical detection of the causes of hypotonic hyponatraemia that are associated with impaired capacity of renal water excretion is greatly facilitated by assessing ECF volume (Table 2). The causes can be categorized into three groups: (a) decreased ECF volume; (b) essentially normal ECF volume; and (c) increased ECF volume (oedema states). Importantly, all conditions of impaired renal excretion of water with the exception of renal failure are characterized by high plasma concentration of vasopressin despite hypotonicity (i.e. non-osmotic stimulation). It must be emphasized, however, that despite the presence of a water excreting defect, hyponatraemia will not develop in these patients unless water intake exceeds the capacity of renal water excretion (plus insensible losses).

Hyponatraemia with decreased ECF volume

It is usually simple to diagnose ECF volume contraction in patients with dilutional hyponatraemia. The patient's history allows the clinician to determine whether sodium loss is of renal or extrarenal origin. Volume depletion can be associated with normal supine blood pressure but an

orthostatic fall of the systolic level greater than 15 mm Hg; in addition, an orthostatic increase in heart rate of greater than 15 beats/min and diminished jugular venous pressure can be observed. More severe volume depletion can lead to supine hypotension, reduced tissue perfusion, and diminished skin turgor. Ocular pressure can also decrease and mucous membranes become dry. However, haemodynamic signs of volume depletion are only manifest when volume contraction is quite acute or severe, as retention of water can ameliorate the severity of the volume depletion (Fig. 4e). An increase in serum creatinine and a proportionately greater increase in blood urea nitrogen concentration are typically present evidencing the associated reduction in glomerular filtration rate and augmented renal urea reabsorption. Urine sodium concentration is typically less than 20 mmol/l when volume depletion is of extrarenal origin but greater than 20 mmol/l when the kidneys are the source of the sodium loss.

The principal causes of renal salt-wasting are diuretic agents, osmotic diuresis (due to glucose, urea, or mannitol), adrenal insufficiency, bicarbonaturia, and ketonuria (Table 2). The most common cause of mild hyponatraemia (serum $[Na^+] \geq 130$ mmol/l) is diuretic therapy with a thiazide drug, or less frequently, a loop agent, but clinical evidence of volume depletion might not be present. The mechanisms of diuretic-induced hyponatraemia include ADH release caused

Table 2 Causes of hypotonic hyponatraemia

Impaired capacity of renal water excretion		
Decreased volume of extracellular fluid	Essentially normal volume of extracellular fluid	Increased volume of extracellular fluid
Renal sodium loss	Thiazide diuretics ^a	Congestive heart failure
Diuretic agents	Hypothyroidism	Cirrhosis
Osmotic diuresis (glucose, urea, mannitol)	Adrenal insufficiency	Nephrotic syndrome
Adrenal insufficiency	Syndrome of inappropriate secretion of antidiuretic hormone	Renal failure (acute or chronic)
Cerebral salt-wasting	Postoperative hyponatraemia	Pregnancy
Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)	Decreased excretion of solutes	
Ketonuria	Beer potomania	
Extrarenal sodium loss	Tea-and-toast diet	
Diarrhoea		
Vomiting		
Blood loss		
Excessive sweating (e.g. in marathon runners)		
Fluid sequestration in 'third space'		
Bowel obstruction		
Peritonitis		
Pancreatitis		
Muscle trauma		
Burns		
Excessive water intake		
Primary polydipsia ^b		
Dilute infant formula		
Sodium-free irrigant solutions (used in hysteroscopy, laparoscopy, or transurethral resection of the prostate) ^c		
Accidental intake of large amounts of water (e.g. during swimming lessons)		
Multiple tap-water enemas		

^a Sodium depletion, potassium depletion, stimulation of thirst, and impaired urinary dilution are implicated.

^b Often a mild reduction in the capacity for water excretion is also present.

^c Hyponatraemia is not always hypotonic.

by volume depletion, decreased fluid delivery to the diluting segment, interference with urinary dilution by the drug, and potassium depletion. Osmotic diuresis from uncontrolled DM, high urea excretion due to high protein feeding, or mannitol administration also produces renal salt wasting; yet renal water losses in excess of sodium plus potassium losses can lead to serum hypertonicity if replacement fluid intake is inadequate. Adrenal insufficiency and isolated mineralocorticoid deficiency cause hypovolaemic hyponatraemia, although in some instances, particularly with isolated glucocorticoid deficiency, patients might have hyponatraemia with an essentially normal ECF volume. Bicarbonaturia secondary to renal tubular acidosis or during the disequilibrium stage of vomiting results in renal sodium loss and impaired water excretion, potentially leading to dilutional hyponatraemia. In diabetic, alcoholic, or fasting ketoacidosis, ketonuria causes obligatory sodium and potassium loss. Cerebral salt wasting, often confused with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), is characterized by dilutional hyponatraemia, renal loss of sodium chloride, and volume depletion in a patient with intracranial disease (Atkin *et al.* 1996). This syndrome of unclear pathogenesis (natriuresis has been attributed to a brain natriuretic factor or decreased sympathetic activity) is observed most commonly in neurosurgical patients and those suffering a subarachnoid haemorrhage. Cerebral salt wasting usually resolves within a few weeks. Salt-wasting nephropathy refers to a condition of volume depletion and associated hyponatraemia observed in patients with advanced chronic renal insufficiency (glomerular filtration rate < 15 ml/min) receiving a low sodium diet. Renal salt wasting also occurs in the recovery phase of acute tubular necrosis and in post-obstructive diuresis.

The causes of hypotonic hyponatraemia secondary to extrarenal sodium loss include vomiting, diarrhoea, gastrointestinal or other sources of blood loss, excessive sweating (e.g. marathon runners), and fluid sequestration in 'third space' (Table 2). Gastrointestinal fluid losses are the most common causes of ECF volume depletion in clinical practice; they result in hyponatraemia or hypernatraemia depending on the composition of fluid losses and the patient's water intake. The gastrointestinal fluid lost, especially in states of secretory diarrhoea (e.g. cholera), is largely isotonic despite the variable concentration of sodium and potassium (i.e. sodium-rich secretory diarrhoea has a low potassium concentration and vice versa such that the sum of the concentrations of the two electrolytes is approximately constant and isotonic with serum) (Shiau *et al.* 1985). Replacement of gastrointestinal losses with fluid of low electrolyte content causes hyponatraemia.

In contrast to secretory diarrhoeas, most viral and bacterial intestinal infections generate diarrhoeal fluid losses of low electrolyte content (sodium plus potassium concentration between 40 and 100 mmol/l); organic solutes account for the remaining osmoles (Teree *et al.* 1965). Loss of fluid with a low electrolyte content tends to produce hypernatraemia (unless sufficient water replacement is provided). Use of purgative agents for colon cleansing in preparation for colonoscopy can lead to symptomatic hyponatraemia; its pathogenesis probably involves fecal electrolyte loss, impaired water excretion due to ADH release, and a large water intake for cleansing purpose.

Sweating is unlikely to cause sufficient sodium losses to generate hypotonic hyponatraemia unless extreme sodium restriction is in effect. However, the recent popularity of marathon running is responsible for the regular occurrence of cases of acute hyponatraemia (at times severe and symptomatic) due to the dermal loss of sodium in

association with aggressive water ingestion (Frizzell *et al.* 1986). Reduced splanchnic blood flow during marathon running might prevent water absorption until completion of the race, when the abrupt absorption of a large amount of water generates hypotonicity. Important causes of fluid sequestration in 'third space' and resultant hypovolaemia include bowel obstruction, peritonitis, pancreatitis, muscle trauma, and burns.

Depletion of potassium accompanies many disorders associated with volume contraction of renal or extrarenal origin, especially diuretic treatment and diarrhoeal diseases. As indicated above, this potassium deficit contributes to the development of hypotonic hyponatraemia (Eq. 5).

Hyponatraemia with essentially normal ECF volume

Thiazide diuretics Some patients with thiazide-induced hyponatraemia appear euvolaemic, their blood pressure is normal or elevated (e.g. when the diuretic has been given to treat hypertension), BUN and serum creatinine are normal, but hypokalaemia is always present and at times severe. The pathogenesis of hyponatraemia includes water retention combined with sodium and potassium losses (Fichman *et al.* 1971). Particularly susceptible are the elderly, especially women. Predisposed individuals develop hyponatraemia within hours after a single dose; body weight increases, probably reflecting stimulation of thirst and impairment of renal water excretion. A rare complication of thiazide administration, this type of hyponatraemia represents one of the most common causes of severe hyponatraemia in adults, given the widespread use of thiazides. Hyponatraemia rapidly corrects upon discontinuation of the drug.

Hypothyroidism Severe hypothyroidism commonly leads to hypotonic hyponatraemia that corrects with thyroid replacement therapy. Patients appear euvolaemic and their laboratory findings are similar to those of the SIADH, excluding thyroid-specific findings (Hanna and Scanlon 1997).

Adrenal insufficiency Patients with Addison's disease (primary adrenal insufficiency) can develop hypovolaemic hyponatraemia due to renal salt wasting. However, some patients with Addison's disease and those with isolated corticotrophin deficiency develop euvolaemic hyponatraemia. Glucocorticoid deficiency increases vasopressin secretion in these patients, as glucocorticoids inhibit vasopressin release (Zimmerman *et al.* 1987). Hyperkalaemia is characteristically absent in pure glucocorticoid deficiency but commonly present in other forms of adrenal insufficiency and can be a helpful diagnostic finding. Swift correction of the water excreting defect follows hormonal replacement therapy.

Syndrome of inappropriate secretion of antidiuretic hormone This syndrome represents the most common cause of euvolaemic hypotonic hyponatraemia in clinical practice (Bartter and Schwartz 1967; Verbalis 1995). Vasopressin secretion in patients with SIADH is independent of osmotic or haemodynamic stimuli, resulting in water retention. However, control of sodium balance remains largely intact, urinary sodium excretion reflecting sodium intake. Thus, on physical examination, the ECF volume appears normal, patients being oedema free. Serum $[Na^+]$ is usually between 125 and 135 mmol/l and relatively stable; serum $[Cl^-]$ is also reduced but potassium and total CO_2 are within normal limits. The stability of serum sodium reflects the phenomenon of 'vasopressin escape', which in rats is mediated by a marked

decrease in the expression of the aquaporin-2 water channel (Ecelbarger *et al.* 1997). The diagnosis of SIADH rests on the presence of hypotonic hyponatraemia coupled with inappropriate urinary concentration (urine osmolality > 100 mOsm/kg H₂O), clinical euvoemia, a high urinary [Na⁺] (>30 mmol/l) while on a normal sodium intake, normal glomerular filtration rate, and absence of diuretic use, adrenal insufficiency (cortisol deficiency), or hypothyroidism.

In some patients, firming up the diagnosis of SIADH might require evaluation of plasma ADH, and the response to a water load test or volume expansion. Findings consistent with the diagnosis of SIADH include elevated ADH despite serum hypotonicity, inability to decrease urine osmolality to less than 100 mOsm/kg H₂O in response to a water load and to excrete at least 80 per cent of the load within 4 h, and failure to correct the hyponatraemia with volume expansion (e.g. isotonic saline) but improvement after water restriction.

Malignancies, most commonly small-cell lung carcinoma, but also olfactory neuroblastoma and tumours of the pancreas and duodenum, cause SIADH because of ectopic ADH production by the tumour (Kim *et al.* 1996). Conversely, excessive release of ADH of hypothalamic origin is observed in the SIADH associated with various central nervous disorders (acute psychosis, trauma, stroke, haemorrhage, and inflammatory and demyelinating diseases). The mechanisms leading to SIADH in patients with pulmonary disorders are not clear. Human immunodeficiency virus (HIV) infection complicated by pneumocystis carinii pneumonia, central nervous system infections, or malignancies account for a growing number of patients with the SIADH (Vitting *et al.* 1990). Hyponatraemia in symptomatic HIV infection can also result from adrenal insufficiency or volume depletion (e.g. gastrointestinal fluid losses) (Piedrola *et al.* 1996). Table 3 lists the causes of the SIADH.

Drug-induced hyponatraemia Diuretic agents, largely thiazides, represent the drugs responsible for most cases of drug-induced hyponatraemia. However, other drugs can cause hyponatraemia by acting as ADH analogues (e.g. desmopressin, oxytocin), stimulating the release of ADH, potentiating the renal action of ADH, or by unknown

mechanisms. Table 1 lists drugs other than diuretics that can cause hyponatraemia.

Postoperative hyponatraemia Postoperative hyponatraemia develops because vasopressin secretion persists in patients receiving excessive amounts of electrolyte-free water (5 per cent dextrose in water, hypotonic saline) (Gowrishankar *et al.* 1998). Pain, severe nausea, and frequently, certain medications trigger vasopressin release. Most patients are clinically euvoemic and asymptomatic. However, severe symptomatic hyponatraemia can cause lethal complications (Chung *et al.* 1986).

Transient hypotonic hyponatraemia with a mean decrease in serum [Na⁺] of about 5 mmol/l has been observed in the first few hours after routine cardiac catheterization, but it largely corrects by 24 h. Administration of hypotonic fluids during the procedure together with impaired urine dilution caused by stress, medication, or underlying disease (e.g. heart failure) could explain the hyponatraemia (Aronson 2002).

Hyponatraemia caused by decreased excretion of solutes Low solute excretion limits the maximal urine volume and, therefore, can cause dilutional hyponatraemia if associated with a high water intake (Fox 2002). Prime examples of this type of hyponatraemia are the tea-and-toast diet, observed especially in elderly individuals of poor means, other extreme diets, and beer potomania. If, for example, daily solute excretion is only 100 mOsm, urine output even at maximal urine dilution (50 mOsm/kg H₂O) would be 2 l/day; fluid intake exceeding 2.5 l/day (to account for insensible losses) will cause water retention and hypotonic hyponatraemia. Lack of other dietary intake accounts for the very low solute load in beer potomania (Thaler *et al.* 1998). Refeeding corrects the hyponatraemia.

Hyponatraemia with increased ECF volume

Arterial underfilling in congestive heart failure, cirrhosis, and nephrotic syndrome with severe hypoalbuminaemia can cause hyponatraemia due to excessive ADH secretion (Schrier 1988). This hormonal response is mediated through the carotid baroreceptors that

Table 3 Causes of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)^a

Malignancies	Central nervous system disorders	Pulmonary conditions
Pulmonary/mediastinal	Head trauma	Pneumonia
Bronchogenic carcinoma	Acute psychosis	Lung abscess
Mesothelioma	Delirium tremens	Tuberculosis
Thymoma	Mass lesions	Aspergillosis
Digestive system	Tumour; brain abscess;	Acute respiratory failure
Carcinoma of the pharynx,	subdural haematoma	Positive-pressure ventilation
stomach, duodenum, pancreas	Inflammatory and demyelinating diseases	Chronic obstructive
Genitourinary	Encephalitis; meningitis	pulmonary disease
Carcinoma of the uterus,	Systemic lupus erythematosus	Cystic fibrosis
prostate, bladder, ureter	Guillain-Barré syndrome	
Blood/lymphatic	Spinal cord lesions	
Leukaemia, lymphoma	Multiple sclerosis	
Other	Miscellaneous	
Ewing tumour	Stroke	
	Haemorrhage	
	Pituitary stalk section	
	Infection with the human	
	immunodeficiency virus (HIV)	

^a Many drugs acting through various mechanisms can lead to a syndrome that resembles SIADH (see Table 1).

detect a reduction in arterial stretch or pressure and overcome the inhibitory effect of hypotonicity on vasopressin release.

Congestive heart failure Arterial underfilling caused by the fall in cardiac output in patients with heart failure results in neurohormonal activation (renin–angiotensin, vasopressin, and norepinephrine) that impairs renal water excretion and promotes hypotonic hyponatraemia (Dzau and Hollenberg 1984; Benedict *et al.* 1994). In rats with uncompensated heart failure and hyponatraemia, aquaporin-2 water channels (mRNA and protein level) increase in collecting duct principal cells as a consequence of increased plasma ADH (Xu *et al.* 1997). Hyponatraemia is common in patients with severe congestive heart failure (New York Heart Association classes 3 and 4). In such patients, serum $[Na^+]$ lower than 130 mmol/l prognosticates a short life expectancy unless cardiac function improves (Leier *et al.* 1994). A therapeutic regimen that combines water restriction, an angiotensin-converting enzyme (ACE) inhibitor, and a loop diuretic might improve or correct the hyponatraemia (Dzau and Hollenberg 1984).

Cirrhosis Renal water handling is normal in the early stages of cirrhosis prior to the development of ascites. As the liver disease progresses, ADH secretion increases, thus predisposing to hyponatraemia (Tsuboi *et al.* 1994). At this stage, vasodilation of the splanchnic circulation and possibly additional territories augments ADH release even though ECF volume is substantially increased (Schrier *et al.* 1988). The reduction in renal blood flow observed in advanced cirrhosis (the result of marked splanchnic vasodilation and neurohormonal activation of the renin–angiotensin and sympathetic nervous systems) appears to have a lesser role in the impaired renal water excretion. The likelihood of developing hyponatraemia increases in patients with cirrhosis who are heavy beer drinkers (beer potomania) or those who develop volume depletion due to aggressive diuretic therapy or large volume paracentesis in the absence of peripheral oedema. A serum $[Na^+]$ less than 130 mmol/l carries a poor prognosis and values lower than 125 mmol/l are found in endstage liver disease. Hyponatraemia in cirrhosis is most commonly asymptomatic although it might worsen hepatic encephalopathy (Papadakis *et al.* 1990).

Nephrotic syndrome Impaired renal water excretion and mild hyponatraemia can be observed in patients with nephrotic syndrome. The pathophysiological mechanism is probably different in patients with preserved renal function (e.g. minimal change nephrotic syndrome) than in those with decreased glomerular filtration rate. Vasopressin release triggered by a decrease in effective circulating arterial volume (i.e. arterial underfilling) appears to be at fault in patients with nephrotic syndrome, severe hypoalbuminaemia, and preserved renal function. Conversely, the renal disease itself probably accounts for the impaired renal water excretion in nephrotic patients with hypofiltration. Aggressive use of diuretics can be responsible for generating severe hyponatraemia in nephrotic patients.

Renal failure Hyponatraemia can occur with advanced acute or chronic renal failure. In these patients, free water excretion is mainly limited by the reduced glomerular filtration rate. As an example, when the glomerular filtration rate is at 10 ml/min (14 l/day) with approximately 20 per cent of filtrate reaching the diluting segments of the nephron, the maximum electrolyte-free water generation is approximately 2.8 l/day. In advanced renal failure, the minimum urine osmolality can be 200–250 mOsm/kg H_2O despite appropriate suppression of ADH secretion; thus, unrestricted water intake might lead to

hyponatraemia. The higher minimum urine osmolality is due to increased solute excretion per functioning nephron resulting in osmotic diuresis (Fig. 1). Patients with end-stage renal disease on chronic maintenance haemodialysis commonly have substantial accumulation of ECF in the interdialytic period, but they rarely experience severe hyponatraemia; this probably occurs because water intake results from hypertonicity generated by salt ingestion.

Excessive water intake

The normally large renal capacity for water excretion accounts for the relatively uncommon occurrence of dilutional hyponatraemia due to excessive water intake (Table 2). Complete suppression of ADH release in response to a water load causes water diuresis, with a high urine volume and minimum urine osmolality. In a subject excreting 700 mOsm/day of solute, for example, 14 l of water can be eliminated at a minimum urine osmolality of 50 mOsm/kg H_2O over the course of a day. Increased urine output or polyuria (arbitrarily defined as a urine output > 3 l/day) can reflect water diuresis (due to increased water intake or impaired urinary concentration) or increased solute secretion.

Primary polydipsia

Excessive water intake caused by a primary stimulation of thirst represents the underlying defect in primary polydipsia (compulsive water drinking). If ADH control and the urine dilution mechanism were intact, primary polydipsia should not lead to significant hyponatraemia unless water intake is massive, a situation not frequently encountered. Primary polydipsia is often observed in acutely psychotic patients, particularly those with schizophrenia, and in anxious, middle-aged women. Many of these subjects ingest a moderate to large water load that is compounded by a diminished capacity of renal water excretion. Factors that conspire in generating the hyponatraemia include a central defect in thirst regulation (e.g. the tonicity threshold for thirst is lower than that for ADH release, a reversal of normal), an excessive secretion of ADH or renal response to this hormone, and consequences of therapy for mental disease; some antipsychotic medications impair renal water excretion and induce the sensation of a dry mouth that enhances thirst.

Primary polydipsia also occurs with hypothalamic injury affecting the thirst centre as in infiltrating diseases, including sarcoidosis. Other neurological conditions, such as multiple sclerosis and tuberculous meningitis, can cause polydipsia and polyuria. Patients with isolated primary polydipsia have dilute urine with specific gravity less than 1.005 and osmolality less than 150 mOsm/kg H_2O . If the capacity of renal water excretion is impaired, urine is less than maximally dilute. Water restriction represents the short-term measure for managing the hypotonic state; in patients with severe hyponatraemia, medical supervision of fluid restriction is most important to prevent an excessively rapid correction of hyponatraemia that, by itself, might lead to neurological damage (i.e. central pontine myelinolysis).

Symptomatic hyponatraemia due to an acute water load has also been reported in patients undergoing urinary testing for illegal drugs or preparation for a radiological examination. Concurrent diuretic therapy or ADH release induced by stress or nausea might have played a predisposing role in these otherwise normal individuals. The ingestion of recreational drugs, such as the amphetamine Ecstasy (methylenedioxymethamphetamine or MDMA), can lead to life-threatening hyponatraemia presumably due to a combination of increased water intake and nonosmotic (tonicity independent) ADH release.

Hyponatraemia associated with sodium-free irrigant solutions

Sodium-free flushing solutions containing glycine, sorbitol, or mannitol are used during transurethral resection of the prostate or a bladder tumour, hysteroscopy, or endometrial ablation for control of uterine bleeding (Agarwal and Emmet 1994; Istre *et al.* 1994). As much as 20–30 l of irrigant solutions are used and variable amounts enter the circulation during the procedure leading to hyponatraemia. Risk factors for the development of severe hyponatraemia are prolonged surgery, large tissue resection, and irrigant solution introduced under high pressure. The glycine and sorbitol solutions have a low osmolality (165–200 mOsm/kg H₂O) causing a decrease in serum sodium and tonicity that is greatest immediately following irrigant fluid absorption in the patient's circulation. Both glycine and sorbitol are organic solutes that undergo metabolic degradation leaving behind the free water of the irrigant solution; they are also excreted by the kidney. The manifestations of glycine-associated hyponatraemia include early nausea and, in severe cases, neurological dysfunction, including confusion, muscle twitching, and seizures. The pathogenesis of these symptoms is unclear, but most likely reflects toxicity from glycine or its metabolic products, including ammonia and serine. Hypotonicity might be largely irrelevant, because administration of mannitol to maintain serum tonicity fails to protect from the neurological manifestations.

The diagnosis of irrigant solution-induced hyponatraemia is derived from the clinical history and the demonstration of an osmolal gap (initially it can exceed 30–60 mOsm/kg H₂O).

Other causes of hyponatraemia due to excessive water intake

Multiple tap water enemas in individuals of small body size can cause substantial hyponatraemia. Feeding infants with dilute formula can

exceed their renal capacity of water excretion resulting in a hypotonic state. Dilutional hyponatraemia can also result from the accidental intake of large amounts of water during swimming lessons (in a sweet-water swimming pool or lake).

Signs and symptoms of hyponatraemia

The manifestations of hypotonic hyponatraemia are largely related to dysfunction of the central nervous system induced by cerebral oedema. They are more conspicuous when the decrease in the serum sodium concentration is large or rapid (i.e. occurring within a period of hours). Nausea and malaise develop at serum [Na⁺] of 120–130 mmol/l. Headache, lethargy, obtundation, and depressed reflexes occur with serum [Na⁺] lower than 120 mmol/l. Seizures, coma, permanent brain damage, brain stem herniation, and respiratory arrest and death develop at lower levels of serum sodium concentration. Severe hyponatraemic encephalopathy most often occurs with excessive water retention in patients who are essentially euvoelaemic (e.g. those recovering from surgery or those with primary polydipsia); prepubertal children and menstruating women appear to be at particular risk (Arieff *et al.* 1992; Ayus *et al.* 1992).

Hypotonic hyponatraemia causes entry of water derived from the interstitial fluid, vascular compartment, and cerebrospinal fluid into the brain, presumably across a water channel (aquaporin-4). Because the surrounding cranium limits expansion of the brain, intracranial hypertension develops, with a risk of brain injury (Fig. 5). Increased intracranial pressure initially reduces the volume of blood within the vault and of the cerebrospinal fluid; in addition, it promotes the exit of brain ECF into the cerebrospinal fluid compartment (Melton *et al.* 1987). Within hours, brain cells lose potassium, sodium, and chloride

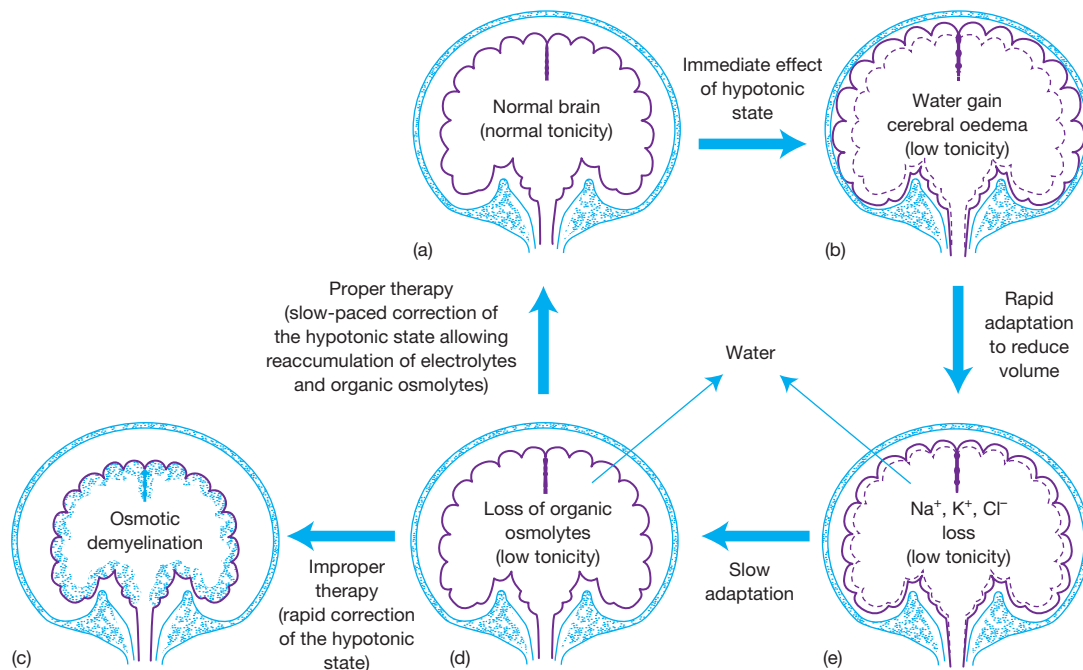


Fig. 5 Effects of hyponatraemia on the brain and adaptive responses. Within minutes after the development of hypotonicity, water gain causes swelling of the brain and a decrease in osmolality of the brain (b). Partial restoration of brain volume occurs within a few hours as a result of cellular loss of electrolytes (rapid adaptation) (c). The normalization of brain volume is completed within several days through loss of organic osmolytes from brain cells (slow adaptation) (d). Low osmolality in the brain persists despite the normalization of brain volume. Proper correction of hypotonicity re-establishes normal osmolality without risking damage to the brain (back to a). Overly aggressive correction of hyponatraemia can lead to irreversible brain damage (osmotic demyelination) (e).

as a result of activation of respective cell membrane channels, thereby promoting partial restoration of cell volume and amelioration of brain swelling (Lien *et al.* 1991). This process is completed via organic solute (osmolytes) loss that occurs as a subsequent step of the volume regulatory response (Fig. 5). Such brain osmolytes include amino acids (glutamine, glutamate, taurine), carbohydrates (myoinositol), and choline compounds (Gullans and Verbalis 1993). The cerebral adaptation to hyponatraemia takes 2–4 days for completion and accounts for the lack of symptoms in many patients with severe chronic hyponatraemia (<120 mmol/l). Nevertheless, brain adaptation is also the source of the risk of central pontine myelinolysis (Fig. 5).

Central pontine myelinolysis

Central pontine myelinolysis or osmotic demyelination is an uncommon but serious condition that can develop one to several days after aggressive treatment of hyponatraemia by any method, including water restriction alone (Tanneau *et al.* 1994; Laureno and Karp 1997). Postoperative patients given large amounts of hypotonic fluids and patients with thiazide-induced hyponatraemia are particularly susceptible. Also, hepatic failure, chronic alcoholism, potassium depletion, and malnutrition increase the risk of this complication. The pathogenesis of this entity remains unclear, but potential mechanisms include ionic overshoot, delayed osmolyte reaccumulation, and disruption of the blood–brain barrier. Presumably, the cellular loss of solutes during adaptation to hyponatraemia increases the risk of damage from shrinkage of the brain in response to a swift elevation in the serum $[\text{Na}^+]$ (overly rapid correction of hyponatraemia). Osmotic shrinkage of axons might disrupt interaction with their myelin sheaths inducing demyelination. The demyelination process is often diffuse but sometimes spares the pons. Patients with osmotic demyelination exhibit various neurological manifestations, such as quadriplegia, pseudobulbar palsy, seizures, and coma, and even death. The diagnosis is made by magnetic resonance imaging, a technique more sensitive than CT scanning, although detection of osmotic demyelination with any technique might

take 1–2 weeks from the onset of the syndrome (Brunner *et al.* 1990). Outcome is often fatal, while survivors are commonly left with permanent brain damage. Effective treatment has not been identified although promising results in three patients treated with aggressive plasmapheresis have been reported (Bibl *et al.* 1999).

Treatment of hypotonic (dilutional) hyponatraemia

Restriction of electrolyte-free fluid intake to less than the combined fluid losses (urinary, stool, insensible losses) gradually increases the serum $[\text{Na}^+]$ and tonicity and should be used in all patients with dilutional hyponatraemia (Adrogué and Madias 2000a; Gross 2001). In patients with hyponatraemia from excessive water intake, simply reducing water ingestion to usual amounts is sufficient to correct the disorder in most cases. In euvoalaemic or oedematous patients, reduction of fluid intake to less than 800 ml/day is usually necessary to produce negative water balance. In hypovolaemic patients, isotonic saline infusion corrects the ECF volume depletion and the associated hyponatraemia; yet, electrolyte-free fluid restriction must also be enforced.

The optimal treatment of hypotonic hyponatraemia balances the risks of hypotonicity against those of therapy (Berl 1990). The presence of symptoms and their severity largely determine the pace of correction.

Symptomatic hypotonic hyponatraemia

Patients who have symptomatic hyponatraemia with concentrated urine (osmolality ≥ 200 mOsm/kg H_2O) and clinical euvoalaemia or hypervolaemia require infusion of hypertonic saline (Table 4). This treatment provides rapid but controlled correction of hyponatraemia. Hypertonic saline is usually combined with frusemide to limit expansion of the ECF volume. Because frusemide-induced diuresis is equivalent to one-half isotonic saline solution, it aids in the correction of hyponatraemia, as do ongoing dermal and respiratory fluid losses; anticipation of these losses should temper the pace of infusion of hypertonic saline. Obviously, electrolyte-free water intake must be withheld. In addition to hypertonic saline, hormone-replacement therapy should be given to patients with

Table 4 Formula for use in managing hyponatraemia and hypernatraemia and characteristics of infusates

Formula ^a		Clinical use
Change in serum $\text{Na}^+ = \frac{[\text{infusate Na}^+ + \text{infusate K}^+] - \text{serum Na}^+}{\text{total body water} + 1}$		Estimate the effect of 1 l of any infusate containing Na^+ and K^+ on serum Na^+
Infusate	Infusate Na^+ (mmol/l)	Extracellular-fluid distribution (%)
5% Sodium chloride in water	855	100 ^b
3% Sodium chloride in water	513	100 ^b
0.9% Sodium chloride in water	154	100
Ringer's lactate solution	130	97
0.45% Sodium chloride in water	77	73
0.2% Sodium chloride in 5% dextrose in water	34	55
5% Dextrose in water	0	40

^a The numerator in the formula is a simplification of the expression $(\text{infusate Na}^+ - \text{serum Na}^+) \times 1 \text{ l}$, with the value yielded by the equation in millimoles per litre. The estimated total body water (in litres) is calculated as a fraction of body weight. The fraction is 0.6 in children, 0.6 and 0.5 in non-elderly men and women, respectively, and 0.5 and 0.45 in elderly men and women, respectively. Normally, extracellular and intracellular fluids account for 40 and 60 per cent of total body water, respectively.

^b In addition to its complete distribution in the extracellular compartment, this infusate induces osmotic removal of water from the intracellular compartment.

suspected hypothyroidism or adrenal insufficiency after blood samples are obtained for diagnostic testing. On the other hand, most patients with hypovolaemia are treated successfully with isotonic saline. Patients with seizures also require immediate anticonvulsant drug therapy and adequate ventilation (Oh *et al.* 1995).

Patients with moderate, symptomatic hyponatraemia, and dilute urine (osmolality < 200 mOsm/kg H₂O) usually require only water restriction and close observation. Examples of such patients are those with isolated primary polydipsia, decreased intake (and excretion) of solutes, or correction of a previously existing water-excretion defect. Severe symptoms (e.g. seizures, coma) call for infusion of hypertonic saline.

There is no consensus about the optimal prescription for treating symptomatic hyponatraemia (Cluitmans and Meinders 1990; Lauriat and Berl 1997; Gross 2001). Nevertheless, correction should be of a sufficient pace and magnitude to reverse in a timely fashion the most serious manifestations of hypotonicity, but should not be so rapid and large as to pose a risk of developing osmotic demyelination. Physiological considerations indicate that a relatively small increase in the serum sodium concentration, of the order of 5 per cent, should substantially reduce cerebral oedema. Even seizures induced by hyponatraemia can be stopped by rapid increases in serum [Na⁺] that average only 3–7 mmol/l. Most reported cases of osmotic demyelination occurred after correction in excess of 12 mmol/l per day, but isolated cases occurred after corrections of only 9–10 mmol/l in 24 h or 19 mmol/l in 48 h. Altogether, we recommend a targeted rate of correction that does not exceed 8 mmol/l on any day of treatment (Adrogué and Madias 2000a). Within this target, the initial rate of correction can be 1–2 mmol/l/h for several hours in patients with severe symptoms. Should severe symptoms not respond to correction according to the specified target, we suggest that this limit be cautiously exceeded, as the imminent risks of hypotonicity override the potential risk of osmotic demyelination. Recommended indications for stopping the rapid correction of symptomatic hyponatraemia (regardless of the method used) are cessation of life-threatening manifestations, moderation of other symptoms, or achievement of a serum [Na⁺] of 125–130 mmol/l (or even lower if the base-line serum sodium is <100 mmol/l). Long-term management of hyponatraemia (described below under asymptomatic hypotonic hyponatraemia) should then be initiated. Should one exceed the recommended target of correction, animal data and a clinical case support the relowering of the serum [Na⁺] via administering water and vasopressin to prevent development of osmotic demyelination (Soupart *et al.* 1994, 1999). Although faster rates of correction can be tolerated safely by most patients with acute (<48 h) symptomatic hyponatraemia, there is no evidence that such an approach is beneficial (Cheng *et al.* 1990). Moreover, ascertaining the duration of hyponatraemia is usually difficult.

The rate of infusion of the selected solution can be derived expediently by applying a simple formula (Adrogué and Madias 1997) (Table 4). The change in serum [Na⁺] induced by the retention of 1 l of a given solution can be estimated as follows:

$$\text{Change in serum Na}^+ = \frac{[\text{infusate Na}^+ + \text{infusate K}^+] - \text{serum Na}^+}{\text{total body water} + 1} \quad (6)$$

Dividing the change in serum sodium targeted for a given treatment period by the output of this formula determines the volume of

infusate required, and hence the rate of infusion. One should use this and other formulae with caution, as it is assumed that the apparent space of distribution of the infused sodium and potassium is total body water, and that no water, sodium, or potassium is lost or gained from the body other than the administered infusate. The apparent space into which administered sodium and potassium distribute might well be smaller than total body water depending on the rate at which the infused electrolytes enter the intracellular compartment. Also, ongoing sodium, potassium, and water losses in gastrointestinal secretions, drainage fluids, or urine during the treatment period cannot be anticipated by Eq. (6) and other formulae. As a general framework, these formulae provide quantitative projections for guiding the repair of abnormalities in serum sodium concentration. Because of uncertainties about the effects of the infusate as well as intercurrent fluid losses, serum [Na⁺] should be checked frequently during treatment and the fluid prescription adjusted accordingly. We do not recommend use of the following conventional formula for the correction of hyponatraemia:

$$\begin{aligned} \text{Sodium requirement} \\ &= \text{total body water} \times (\text{desired serum [Na}^+]) \\ &\quad - \text{current [Na}^+] \end{aligned} \quad (7)$$

The conventional formula requires a relatively complicated procedure to convert the amount of sodium required to raise the sodium concentration to an infusion rate for the selected solution. Of course, Eq. (7) shares all the limitations described for the recommended formula (Eq. 6). Further, the conventional formula (Eq. 7) underestimates the sodium requirement, as the volume of the infusate retains a considerable fraction of the administered sodium load (volume of infusate multiplied by the final serum [Na⁺]). Table 5 depicts illustrative cases of symptomatic hyponatraemia and their management.

Asymptomatic hypotonic hyponatraemia

In some patients with asymptomatic hyponatraemia, the main risk of complications emanates not from the disorder itself, but from its correction phase. This is true of patients who stop drinking large amounts of water and those whose water-excretion defect is repaired (e.g. repletion of ECF volume, discontinuation of offending drugs). If excessive diuresis occurs so that the projected rate of spontaneous correction exceeds that recommended for patients with symptomatic hyponatraemia, hypotonic fluids or desmopressin can be administered.

In contrast, there is no such risk associated with the asymptomatic hyponatraemia that accompanies oedema states or the SIADH because of the prevailing defect of water excretion. Water restriction (to <800 ml per day) is the mainstay of long-term management, with the goal being induction of negative water balance. In severe cardiac failure, optimization of haemodynamics by several measures, including the use of ACE inhibitors, can increase excretion of electrolyte-free water and mitigate hyponatraemia. Further, ACE inhibitors enhance the secretion of renal prostaglandins that antagonize the effects of ADH on the collecting tubule. Loop, but not thiazide, diuretics reduce urine concentration and augment excretion of electrolyte-free water, thereby permitting relaxation of fluid restriction. In the SIADH, but not in oedema disorders, loop diuretics should be combined with an abundant sodium intake (in the form of dietary sodium or salt tablets), a treatment that augments water loss. If these measures fail, 600–1200 mg of demeclocycline per day can help by inducing nephrogenic diabetes insipidus (Verbalis 1995). Renal function should be monitored,

Table 5 Managing symptomatic hyponatraemia: illustrative cases

Case No.	Time (h)	Data	Diagnosis/treatment plan	Fluid prescription
1	0	28-year-old woman with stupor and grand-mal seizures 2 days after appendectomy; euvolaemic; weight 67 kg; $[Na^+]$ 113 mmol/l, $[K^+]$ 4.5 mmol/l, S _{osm} 229 mOsm/kg H ₂ O, U _{osm} 550 mOsm/kg H ₂ O	Postoperative hyponatraemia; diazepam 20 mg IV, phenytoin 250 mg IV, laryngeal intubation, mechanical ventilation, withholding of water, frusemide 20 mg IV, 3% NaCl to increase $[Na^+]$ by 3 mmol/l over 2 h	TBW, $0.5 \times 67 = 33.5$ l $\Delta[Na^+] = \frac{513 - 113}{33.5 + 1} = 11.6$ mmol/l per 1 l infusate For a goal of $\Delta[Na^+]$ 3 mmol/l/2 h, $3/11.6 = 0.259$ l/2 h is required, or ~130 ml/h
	2	No further seizure episodes; she responds to pain but not to commands; $[Na^+]$ 116 mmol/l	3% NaCl to increase $[Na^+]$ by 3 mmol/l over 6 h	For a goal of $\Delta[Na^+]$ 3 mmol/l/6 h, $3/11.6 = 0.259$ l/6 h is required, or ~43 ml/h
	8	No seizure activity, patient responds to simple commands; $[Na^+]$ 120 mmol/l	Discontinue 3% NaCl Continue to withhold water Close monitoring	
2	0	60-year-old man with small-cell lung carcinoma, who presents with severe confusion and lethargy; euvolaemic; weight 72 kg; $[Na^+]$ 108 mmol/l, $[K^+]$ 4.0 mmol/l, BUN 8 mg/dl, creatinine 0.6 mg/dl, S _{osm} 222 mOsm/kg H ₂ O, U _{osm} 625 mOsm/kg H ₂ O	Tumour-induced SIADH; withholding of water frusemide 20 mg IV 3% NaCl to increase $[Na^+]$ by 5 mmol/l over 12 h	TBW, $0.6 \times 72 = 43$ l $\Delta[Na^+] = \frac{513 - 108}{43 + 1} = 9.2$ mmol/l per 1 l infusate For a goal of $\Delta[Na^+]$ 5 mmol/l/12 h, $5/9.2 = 0.543$ l/12 h is required, or ~45 ml/h
	12	Mildly lethargic but easily arousable; $[Na^+]$ 114 mmol/l	Discontinue 3% NaCl Continue to withhold water Close monitoring	

Table 5 Continued

Case No.	Time (h)	Data	Diagnosis/treatment plan	Fluid prescription
3	0	70-year-old woman with vomiting and diarrhoea for 4 days, who presents with lethargy but no focal neurologic deficits; hypovolaemic, supine BP 98/58 mmHg; weight 75 kg; $[\text{Na}^+]$ 112 mmol/l, $[\text{K}^+]$ 2.4 mmol/l, $[\text{HCO}_3^-]$ 30 mmol/l, BUN 45 mg/dl, creatinine 1.4 mg/dl, S _{osm} 242 mOsm/kg H ₂ O, U _{osm} 650 mOsm/kg H ₂ O	Hypovolaemic hyponatraemia; potassium depletion; prerenal azotaemia; withholding of water; volume repletion, potassium repletion, increase $[\text{Na}^+]$ by no more than 8 mmol/l over 24 h	TBW, $0.45 \times 75 = 34$ l Selected infusate is 0.9% NaCl containing 30 mmol/l of KCl $\Delta[\text{Na}^+] = \frac{(154 + 30) - 112}{34 + 1} = 2.0$ mmol/l per 1 l infusate Administer 1 l/h for the next 2 h
	2	Moderate drowsiness; supine BP 106/64 mmHg; $[\text{Na}^+]$ 117 mmol/l, $[\text{K}^+]$ 3.1 mmol/l	Withholding of water; continue volume and potassium repletion; note that restoration of ECF volume will eliminate non-osmotic stimulus to ADH release thereby promoting rapid excretion of dilute urine	Switch infusate to 0.45% NaCl containing 30 mmol/l of KCl $\Delta[\text{Na}^+] = \frac{(77 + 30) - 117}{34 + 1} = -0.3$ mmol/l per 1 l infusate Administer 100 ml/h for the next 12 h
	6	Mild drowsiness; supine BP 112/68 mmHg; $[\text{Na}^+]$ 118 mmol/l, $[\text{K}^+]$ 3.2 mmol/l	Despite the formula's estimate that this infusate will not change $[\text{Na}^+]$ measurably at 100 ml/h, $[\text{Na}^+]$ continues to increase (the sum of sodium and potassium concentrations of the urine must be lower than that of the infusate)	Continue present infusate at 100 ml/h
	12	Minimal drowsiness; supine BP 126/72 mmHg; $[\text{Na}^+]$ 119 mmol/l, $[\text{K}^+]$ 3.4 mmol/l	Prevent further correction of $[\text{Na}^+]$ over the next 12 h	Switch infusate to 5% dextrose containing 30 mmol/l of KCl at a rate matching urinary output

because demeclocycline has nephrotoxic effects, especially in patients with cirrhosis. Moreover, the drug imposes the risk of hyponatraemia in patients who do not take in sufficient water. Management of chronic hyponatraemia will be helped by the anticipated introduction of promising oral agents that antagonize the effect of vasopressin on the V_2 receptor. Encouraging results have been obtained in hyponatraemic patients with cardiac failure, cirrhosis, or the SIADH (Serradeil-Le Gal *et al.* 1996; Saito *et al.* 1997).

Treatment of non-hypotonic hyponatraemia

Corrective measures for non-hypotonic hyponatraemia are directed at the underlying disorder rather than at the hyponatraemia itself. Administration of insulin is the basis of treatment for uncontrolled DM, but deficits of water, sodium, and potassium should also be corrected. Frusemide hastens the recovery of patients who absorb irrigant solutions; if renal function is impaired, haemodialysis is the preferred option.

Common errors in management

Although water restriction ameliorates all forms of hyponatraemia, it is not the optimal therapy in all cases. Hyponatraemias associated with depletion of ECF volume require, in addition to fluid restriction, correction of the prevailing sodium deficit. On the other hand, isotonic saline is unsuitable for correcting the hyponatraemia of the SIADH; if administered, the resulting rise in serum sodium is both small and transient, with the infused salt being excreted in concentrated urine, thereby worsening net retention of water and hyponatraemia. Although uncertainty about the diagnosis occasionally justifies a limited trial of isotonic saline, attentive follow-up is needed to confirm the diagnosis before substantial deterioration occurs. Great vigilance is required to recognize and diagnose hypothyroidism and adrenal insufficiency, as these disorders tend to masquerade as cases of the SIADH. The presence of hyperkalaemia should always alert the physician to the possibility of adrenal insufficiency.

Whereas patients with persistent asymptomatic hyponatraemia require slow-paced management, those with symptomatic hyponatraemia must receive rapid but controlled correction. Prudent use of hypertonic saline can be life-saving, but failure to follow the recommendations for treatment outlined above can cause devastating and even lethal consequences.

Hyponatraemia that is acquired in the hospital is largely preventable. A defect of water excretion can be present on admission, or it can worsen or develop during the course of hospitalization as a result of several antidiuretic influences (e.g. medications, organ failure, and the postoperative state). The presence of such a defect notwithstanding, hyponatraemia will not develop as long as the intake of electrolyte-free water does not exceed the capacity for renal water excretion plus stool and insensible losses. Thus, hypotonic fluids must be supplied carefully to hospitalized patients.

Hyponatraemia

Hyponatraemia, defined as a serum sodium concentration greater than 145 mmol/l, 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. Therefore, hyponatraemia invariably denotes hypertonic hyperosmolality and always causes cellular dehydration, at least transiently (Fig. 6). The resultant morbidity can be

inconsequential, serious, or even life-threatening. Hyponatraemia frequently develops in hospitalized patients as an iatrogenic condition. Some of its most serious complications result not from the disorder itself but from its inappropriate treatment (Palevsky *et al.* 1996).

Sustained hyponatraemia occurs only when thirst or access to water is impaired. The groups at highest risk are thus patients with altered mental status, intubated patients, infants, and elderly persons. Hyponatraemia in infants usually results from vomiting, a condition that causes hypotonic fluid loss while preventing retention of ingested fluid. In elderly persons, hyponatraemia is usually associated with infirmity or febrile illness (Adrogué and Madias 2000b); the elderly also have thirst impairment. Frail nursing home residents and hospitalized patients are prone to hyponatraemia because they depend on others to satisfy their water requirements. People without access to water, such as those stranded in the desert or on an ocean raft, and those abandoned in a confined space are also at risk of hyponatraemia.

Hyponatraemia represents a deficit of water in relation to the body's sodium stores, which can result from net water loss or hypertonic sodium gain (Table 6). Net water loss accounts for the majority of cases of hyponatraemia. It can occur without associated sodium deficit (pure water loss) or with sodium depletion (hypotonic fluid loss) (Fig. 6). Pure water is lost via dermal, respiratory, or renal routes (Table 6). Contrary to common belief, hyponatraemia caused by pure water loss is associated with a contracted, not normal, ECF volume (Fig. 6a and b), although the ECF contraction is often not clinically evident. In this setting, the sodium content of the ECF remains unaltered, yet one out of each 2.5 l of water loss derives from the ECF compartment. ECF contraction is, of course, magnified when hyponatraemia is caused by hypotonic fluid losses, as sodium content is the primary determinant of the size of the ECF compartment (Fig. 6c). Importantly, hypotonic fluid losses containing both sodium and potassium, as they typically occur during osmotic diuresis and use of cathartics, including lactulose therapy, lead to additional contraction of the ICF compartment (Fig. 6d). Hypertonic sodium gain usually results from clinical interventions or accidental sodium loading (Table 6 and Fig. 6e). The resultant hyponatraemia is associated with ECF expansion together with contraction of the ICF compartment (Fig. 6e).

Hyponatraemia due to pure water loss

Hypodipsia and unreplaced insensible losses

Decreased thirst perception, termed hypodipsia, is common in elderly individuals, but is seldom the sole cause of hyponatraemia due to unreplaced sensible and insensible fluid losses (Robertson 1984). Hypothalamic lesions caused by vascular disease, tumours, or granulomatous disease (e.g. sarcoidosis) also result in hypodipsia, sometimes accompanied by diabetes insipidus. A different entity, known as essential hyponatraemia, is characterized by hypodipsia associated with an upward resetting of the central osmoreceptors. In these patients, water loading inhibits ADH release in response to volume expansion rather than low serum tonicity; thus, administered water is excreted in the urine and hyponatraemia is perpetuated. Although patients with essential hyponatraemia are generally asymptomatic, chlorpropamide administration might moderate the hyponatraemia by enhancing the renal effects of ADH. Patients with primary aldosteronism maintain a stable serum sodium of the order of 143–147 mmol/l. It is presumed that the prevailing mild volume expansion characteristic of this syndrome causes an upward resetting of the osmostat.

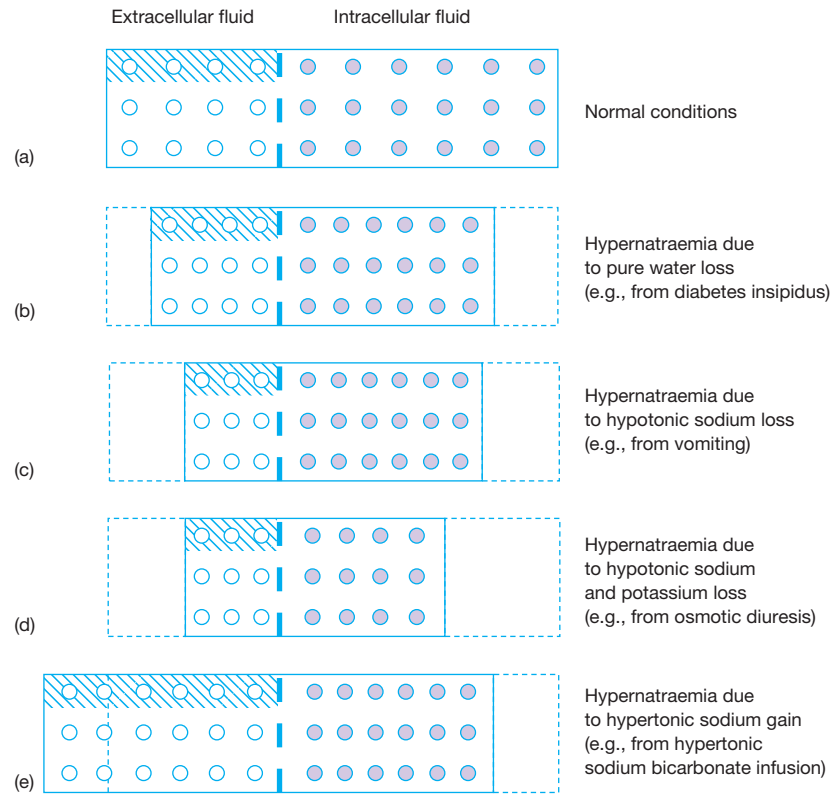


Fig. 6 Extracellular-fluid and intracellular-fluid compartments under normal conditions and during states of hypernatraemia. Normally, the ECF and ICF compartments account for 40 and 60 per cent of total body water, respectively (Panel a). Pure water loss reduces the size of each compartment proportionately (Panel b). Contrary to common belief, the volume of ECF in this setting is reduced, not normal, although the reduction is often not clinically evident. The sodium content of ECF remains unaltered, yet 1 of each 2.5 l of water that is lost is from the ECF compartment. Hypotonic sodium loss causes a relatively larger loss of volume in the ECF compartment than in the ICF compartment (Panel c). Potassium loss in addition to hypotonic sodium loss further reduces the ICF compartment (Panel d). Hypertonic sodium gain results in an increase in ECF but a decrease in ICF (Panel e). In each panel, the open circles denote sodium, and the solid circles denote potassium; the broken line between the two compartments represents the cell membrane, and the shading indicates the intravascular volume.

Table 6 Causes of hypernatraemia

Net water loss		Hypertonic sodium gain
Pure water	Hypotonic fluid	
Unreplaced insensible losses (dermal and respiratory)	Renal causes	Hypertonic sodium bicarbonate infusion
Hypodipsia	Loop diuretics	Hypertonic feeding preparation
Central diabetes insipidus	Osmotic diuresis (glucose, urea, mannitol)	Ingestion of sodium chloride
Nephrogenic diabetes insipidus	Polyuric phase of acute tubular necrosis	Ingestion of sea water
	Postobstructive diuresis	Sodium chloride-rich emetics
	Intrinsic renal disease	Hypertonic saline enemas
	Gastrointestinal causes	Intrauterine injection of hypertonic saline
	Vomiting	Hypertonic sodium chloride infusion
	Nasogastric drainage	Hypertonic dialysis
	Enterocutaneous fistula	Primary hyperaldosteronism
	Diarrhoea	Cushing's syndrome
	Use of osmotic cathartic agents (e.g. lactulose)	
	Cutaneous causes	
	Burns	
	Excessive sweating	

Central diabetes insipidus

Diabetes insipidus signifies production of an inappropriately dilute urine and reflects either abnormal release of ADH (i.e. central diabetes insipidus, CDI) or unresponsiveness of the kidney to this hormone (i.e. nephrogenic diabetes insipidus).

CDI results from functional or structural disorders that suppress ADH secretion (Table 7). Ethanol ingestion, anorexia nervosa, acute fatty liver of pregnancy, and correction of supraventricular tachycardia can lead to polyuria caused by transient depression of ADH release. Conversely, structural damage of the sites involved in ADH secretion (i.e. hypothalamic osmoreceptors, the supraoptic or paraventricular nuclei, and the superior portion of the hypothalamic–pituitary tract) accounts for the majority of CDI cases in clinical practice. Incomplete impairment of vasopressin secretion might cause partial forms of the syndrome. Up to one-half of all cases of CDI are idiopathic and most likely due to autoimmune disease (e.g. antibodies against vasopressin-producing cells). Yet, patients with presumed idiopathic CDI can develop an anterior pituitary endocrinopathy years after diagnosis

Table 7 Causes of diabetes insipidus

Central	Nephrogenic
Head trauma	Hereditary
Postoperative	X-linked (V2 receptor)
Hypophysectomy	Autosomal
Craniopharyngioma	(aquaporin-defect)
Hypothalamic tumours	Specific congenital defects
Brainstem tumours	Vasopressin V2-receptor mutations
Primary: dysgerminoma, craniopharyngioma, suprasellar pituitary tumours	Aquaporin-2 mutations
Metastatic: carcinoma of the breast, carcinoma of the lung, lymphoma, leukaemia	Acquired
Infections	Renal disease
Encephalitis	Chronic renal insufficiency
Meningitis	Polycystic kidney disease
Tuberculosis	Medullary cystic disease
Syphilis	Obstructive uropathy
Vascular	Pyelonephritis
Aneurysms	Sickle-cell disease
Brainstem hypoxia	Amyloidosis
Cerebrovascular accidents	Light-chain disease
Sheehan's syndrome (postpartum pituitary haemorrhage)	Sjögren's syndrome
Granulomatous disease	Sarcoidosis
Sarcoidosis	Electrolyte disorders
Histiocytosis	Hypokalaemia
Autoimmune	Hypercalcaemia
Vasopressin-neurophysin gene mutations	Drug induced
Idiopathic	Lithium
Ethanol ingestion (transient)	Demeclocycline
	Methoxyflurane
	Amphotericin B
	Loop diuretics
	Frusemide
	Ethacrynic acid
	Bumetanide
	Torsemide
	Osmotic diuretics
	Vasopressin antagonists

caused by a pituitary or suprasellar tumour, which might have initially caused the CDI. Neurosurgery or trauma to the hypothalamus and neurohypophysis accounts for a significant fraction of cases of CDI; those with severe damage often exhibit the classic triphasic response. The initial phase consists of polyuria that begins within 24 h from the injury and lasts for 4–5 days; it is caused by depression of ADH release. The second phase is oliguric and also lasts for 4–5 days; it is caused by the slow release of ADH stored in the damaged posterior lobe and can lead to excessive water retention. The third phase consists of permanent CDI. Some patients with milder injury have a partial or even total recovery before completing the three phases (Hensen *et al.* 1999). In children, CDI complicates more than 75 per cent of surgical procedures for craniopharyngiomas. Other causes of CDI include primary or secondary tumours of the brain (e.g. lymphoma, leukaemia, lung carcinoma), hypoxic encephalopathy, infiltrative diseases (such as histiocytosis X), postpartum hypopituitarism, and a familial disease (autosomal dominant inheritance). An even less common inherited disease (autosomal recessive) is the Wolfram or DIDMOAD syndrome characterized by CDI, DM, optic atrophy (OA), and deafness (D). In this syndrome, diabetes insipidus results from loss of neurones in the supraoptic nuclei; defects in chromosome 4 and in mitochondrial DNA have been identified (Inoue *et al.* 1998).

CDI typically presents with sudden polyuria (3–7 l/day) and dilute urine (specific gravity < 1.005, urine osmolality < 150 mOsm/kg H₂O). In an alert patient, hypernatraemia is uncommon because of the associated stimulation of thirst and resulting polydipsia. In fact, the typical patient features polyuria and polydipsia and, at most, a serum sodium in the high-normal range. Conversely, in the comatose or postoperative patient, life-threatening hypernatraemia can develop rapidly because of large unreplaced urinary water losses. Marked hypernatraemia develops when a hypothalamic lesion affects both ADH release and thirst.

Hereditary nephrogenic diabetes insipidus (see also Chapter 5.6)

Hereditary (congenital) nephrogenic diabetes insipidus is an uncommon disorder characterized by normal ADH secretion but resistance to its water-retaining action (Bichet *et al.* 1997). Two forms of the disorder can be encountered, an X-linked dominant defect (usual form) and an autosomal recessive form (rare). The X-linked form is fully expressed almost exclusively in males (who experience marked polyuria that is resistant to vasopressin), whereas the female carriers are usually asymptomatic; occasionally, female carriers become severely symptomatic (especially during pregnancy when placental vasopressinase diminishes serum ADH). The responsible genetic defect involves mutations or deletions in the V2 receptor that result in impaired antidiuretic, vasodilator, and procoagulant responses to vasopressin. The autosomal recessive disorder, observed more frequently in consanguineous marriages, results from a postreceptor defect involving the aquaporin-2 gene. In contrast to patients with the X-linked defect, these patients exhibit normal extrarenal V2 receptor-mediated responses, including vasodilatory and procoagulant (i.e. release from endothelial cells of factor VIIIc and von Willebrand's factor) effects (Hochberg *et al.* 1997).

Acquired nephrogenic diabetes insipidus

A relatively common defect, acquired nephrogenic diabetes insipidus results from a variety of conditions that impair the renal concentrating ability because of resistance of the collecting tubule to ADH or disruption of the countercurrent mechanism; such disruption can originate

from several causes, including decreased sodium chloride reabsorption in the thick ascending limb (medullary portion) or injury of the renal medulla itself. Renal diseases, electrolyte disorders (hypercalcaemia, hypokalaemia), lithium toxicity and other drugs, gestational diabetes insipidus, and dietary abnormalities represent the most important causes of acquired nephrogenic diabetes insipidus.

Renal disease The modest reduction in renal concentrating capacity observed in the elderly and in patients with non-oliguric acute or chronic renal insufficiency is usually not sufficient to generate polyuria, but might produce nocturia (in subjects not drinking at or near bedtime). Maximum urine osmolality limited to only 350–600 mOsm/kg H₂O obligates a higher urine output to excrete the solute load. The defect reflects, at least in part, increased solute excretion per functioning nephron; in experimental chronic renal failure downregulation of the V2 receptor has been observed due to decreased expression of V2 receptor mRNA (Teitelbaum and McGuinness 1995). A severe water conservation defect, manifest as polyuria, is occasionally associated with some renal diseases, including polycystic kidney disease, medullary cystic disease, chronic obstructive uropathy, sickle-cell disease or trait, amyloidosis, Sjögren's syndrome, and light-chain nephropathy.

Hypercalcaemia Hypercalcaemia and lithium toxicity are the most common causes of symptomatic acquired nephrogenic diabetes insipidus in adults. A persistent increase in serum calcium, more than 11 mg/dl, impairs renal concentration capacity through activation of calcium-sensing receptors in the renal tubules and other functional effects, as well as through calcium deposition in the medulla with secondary tubulointerstitial injury (transient or permanent renal medullary damage). Calcium-sensing receptors are activated in two segments of the renal tubule, the thick ascending limb of the loop of Henle (basolateral membrane) and the inner medullary collecting duct (apical membrane). In the loop of Henle, activation of these receptors closes luminal K⁺ channels, with an attendant inhibition of loop reabsorption (sodium chloride, calcium) and a reduction of the medullary osmotic gradient that is normally required for urinary concentration (Wang *et al.* 1996). Further, increased downstream delivery of calcium activates apical calcium-sensing receptors in the inner medullary collecting duct and inhibits the effect of ADH on water permeability. In polyuric hypercalcaemic rats, expression of aquaporin-2 water channels is decreased in renal collecting ducts. A contributory role might also be played by hypercalcaemia-induced generation of prostaglandin E₂ (effect abolished by angiotensin II receptor blockade), which diminishes sodium chloride reabsorption in the thick ascending limb. Normalization of serum calcium usually repairs the nephrogenic diabetes insipidus unless permanent and extensive renal medullary damage had ensued.

Hypokalaemia Severe hypokalaemia caused by potassium depletion impairs the renal concentrating mechanism and stimulates thirst, leading occasionally to polyuria and polydipsia. In experimental animals, the urinary concentrating defect is caused by decreased expression of aquaporin-2 water channels and reduced sodium chloride reabsorption in the thick ascending limb (Marples *et al.* 1996).

Lithium toxicity About 20 per cent of patients receiving long-term treatment with lithium for manic-depressive (bipolar) illness develop symptomatic nephrogenic diabetes insipidus, whereas an additional 30 per cent exhibit milder defects in concentrating capacity. The defect results from lithium entry in collecting duct cells via apical sodium

channels and its interference with ADH action. Postulated mechanisms for such interference include reduction of adenylate cyclase activity, decreased density of vasopressin receptors, and downregulation of aquaporin-2 water channels. Polyuria and polydipsia in a patient receiving chronic lithium therapy should not lead to the presumption of nephrogenic diabetes insipidus; these symptoms could reflect other polyuric syndromes, including primary polydipsia, a not uncommon disorder in psychiatric patients.

Pharmacological agents Several drugs other than lithium are uncommon causes of a clinically relevant urinary concentrating defect. Amphotericin B and methoxyflurane (anaesthetic agent) can cause nephrogenic diabetes insipidus possibly related to their renal toxicity (acute renal failure). The same defect is produced by foscarnet and cidofovir, drugs administered to treat cytomegalovirus infection in HIV-infected patients. Demeclocycline, a tetracycline-related antibiotic used in the treatment of SIADH, decreases the responsiveness of the collecting duct to vasopressin. Vasopressin receptor antagonists include drugs under investigation that antagonize the V2 (antidiuretic) receptor and generate a selective water diuresis.

Gestational diabetes insipidus An increase in plasma vasopressinase, the enzyme that degrades vasopressin, is responsible for this transient syndrome that affects some women during the second part of pregnancy. The excess enzyme is released from the placenta. Desmopressin (dDAVP), a pure V2 receptor agonist, is not degraded by the circulating vasopressinase and is thus effective in managing this syndrome.

Dietary abnormalities Chronic ingestion of large volumes of water (primary polydipsia) and osmotic diuresis (e.g. glucosuria) result in medullary solute washout and impaired urinary concentration capacity. A marked decrease in salt and protein intake also impairs urinary concentration, as sodium and urea (product of protein metabolism) account for most of the osmolality of the renal medulla interstitium.

Differential diagnosis of polyuria

Polyuria is defined as a daily urine output greater than 3 l. It is due to water or solute diuresis. Polyuria due to water diuresis is largely caused by three conditions, primary polydipsia, CDI, and nephrogenic diabetes insipidus. In these conditions, urinary solute excretion is within the normal range but urinary osmolality is usually less than 250 mOsm/kg H₂O. Examples of polyuria caused by solute diuresis include osmotic diuresis (glucose in uncontrolled DM, urea in high-protein feedings) and saline diuresis (volume expansion following saline loading or release of bilateral urinary tract obstruction). In solute diuresis, polyuria is driven by the markedly increased urinary solute load; urinary osmolality usually exceeds 300 mOsm/kg H₂O.

Uncontrolled DM is the most common cause of polyuria in the out-patient setting; determination of blood and urine glucose establishes the diagnosis. After ruling out uncontrolled DM, primary polydipsia is the next most commonly observed cause of polyuria; nephrogenic diabetes insipidus is substantially less common and CDI is truly unusual. A history of gradual onset of polydipsia and polyuria points towards primary polydipsia or nephrogenic diabetes insipidus, whereas an abrupt onset is commonly detected in CDI; nocturia and a desire for ice water are also commonly present in CDI. Information regarding use of drugs or previous illness can help establish the diagnosis. Additional tools to determine the cause of polydipsia and polyuria include the response to a standard dehydration test followed, if necessary, by the administration of vasopressin.

Water restriction raises serum tonicity that normally causes release of ADH and an increase in urine osmolality. Once serum tonicity reaches 290 mOsm/kg H₂O, the antidiuretic effect of endogenous ADH is maximal in normal individuals as well as in patients with primary polydipsia, and urine osmolality exceeds 600 mOsm/kg H₂O (Fig. 7). However, the absence of endogenous ADH in patients with CDI or the lack of response to ADH in patients with nephrogenic diabetes insipidus prevents an appropriate increase in urine osmolality.

A standard dehydration test requires (a) withholding all fluids for 3 h prior to the test and for the duration of the test; (b) measurement of the urine volume and osmolality every hour; and (c) measurement of serum [Na⁺] and osmolality every 2 h. The water restriction test should be discontinued when the urine osmolality exceeds 600 mOsm/kg H₂O, when urine osmolality remains stable on two to three successive measurements despite a rising serum [Na⁺] or osmolality, or when the serum tonicity exceeds 290 mOsm/kg H₂O.

An increase in urine osmolality of more than 600 mOsmol/kg H₂O establishes the diagnosis of primary polydipsia (Fig. 7). Patients with diabetes insipidus, whether central or nephrogenic, fail to reach a urine osmolality level greater than 600 mOsm/kg H₂O in response to a standard water deprivation test (Fig. 7). In addition, their urine osmolality remains stable on two or three successive measurements despite an increasing serum [Na⁺] or osmolality, or their serum tonicity might exceed 290 mOsm/kg H₂O. To ascertain the pathogenesis of the failure to concentrate the urine in response to the water deprivation test, 10 µg of dDAVP by nasal inhalation or 5 units of aqueous vasopressin subcutaneously are administered and urine parameters (osmolality and volume) measured. Although urine osmolality might increase modestly in response to ADH in patients with symptomatic nephrogenic diabetes insipidus, it remains below serum osmolality. In contrast, in CDI, it increases to more than 500 mOsm/kg H₂O. Complete CDI is differentiated from the partial form by the urine osmolality prior to and after vasopressin administration; urine osmolality remains lower

than 200 mOsm/kg H₂O after water deprivation in complete CDI but increases two- to eightfold after vasopressin; urine osmolality usually reaches 300 mOsm/kg H₂O with water deprivation in partial CDI but the response to vasopressin is small (up to 50 per cent increase in urine osmolality) (Fig. 7). In some instances, the water deprivation test and ADH administration fail to identify the precise cause of polyuria and polydipsia because of a considerable overlap in response and the existence of partial defects in ADH secretion. Measurements of plasma vasopressin are then necessary to establish the diagnosis (Fig. 7). Under rare circumstances, even this step might not be diagnostic and a therapeutic trial with desmopressin is required to establish the cause of polyuria.

Hypernatraemia due to hypotonic fluid loss

Unreplaced hypotonic fluid losses of any origin, renal, gastrointestinal, or cutaneous, generate hypernatraemia, the larger the loss, the greater the expected increase in serum sodium. Renal causes of hypotonic fluid loss include loop diuretics, osmotic diuresis (glucose, urea, and mannitol), postobstructive diuresis, polyuric phase of acute tubular necrosis, and intrinsic renal disease. As previously noted, sustained hypernatraemia develops only if thirst or water access is impaired. Patients with uncontrolled DM and large osmotic diuresis caused by glucosuria usually have hyponatraemia rather than hypernatraemia. When hypernatraemia and hyperglycaemia coexist, the patient is usually severely dehydrated and comatose.

Gastrointestinal causes of hypernatraemia include vomiting, nasogastric drainage, enterocutaneous fistula, diarrhoea, and use of osmotic cathartic agents (e.g. lactulose). Vomiting results in loss of hypotonic fluid (gastric juice has [Na⁺] of 20–80 mmol/l and [K⁺] of 5–20 mmol/l); coupled with inability to retain oral water intake, vomiting has the potential for generating substantial hypernatraemia.

Diarrhoea has variable effects on serum sodium as previously described (see hypotonic hyponatraemia secondary to gastrointestinal fluid losses). Because of a limited ability to communicate thirst, severe

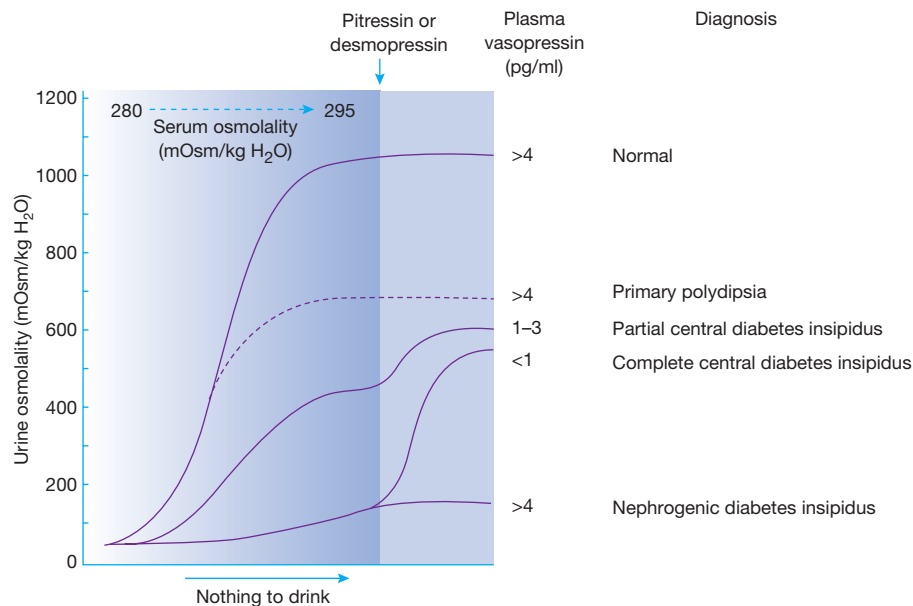


Fig. 7 Response to water deprivation before and after vasopressin administration in normal subjects and in patients with various types of polyuria and polydipsia. (Modified from Valtin, H. *Renal Dysfunction*, Boston: Little Brown, 1979.)

diarrhoea is a common cause of hypernatraemia in infants. Also, diarrhoea can give rise to hypernatraemia in elderly individuals due to the associated hypodipsia. By contrast, unless the gastrointestinal losses are massive or confusion is present, diarrhoea in adults does not cause hypernatraemia. Certain osmotic agents, including sorbitol in managing drug intoxications or lactulose in treating hepatic encephalopathy, commonly generate hypernatraemia in the obtunded or comatose patient given insufficient electrolyte-free fluid.

Excessive fluid loss from the skin or lungs can occur because of fever, exercise, or exposure to high temperature, and leads to hypernatraemia if thirst or access to water is impaired. Insensible fluid loss from the skin or lung occurs by evaporation and, therefore, amounts to pure water loss predisposing to a hypertonic state. Sweat is also a hypotonic fluid ($[\text{Na}^+]$ 30–100 mmol/l and $[\text{K}^+]$ 5–20 mmol/l), therefore predisposing to hypernatraemia. However, as described before for the case of marathon runners, aggressive water intake makes hyponatraemia a more common clinical problem in individuals performing physical exercise than is hypernatraemia.

Hypernatraemia due to hypertonic sodium gain

Severe or extreme hypernatraemia with $[\text{Na}^+]$ greater than 175 mmol/l can be induced by the ingestion or infusion of hypertonic sodium-containing solutions. Hypertonic sodium ingestion can reflect human error involving substitution of sodium chloride for sugar in a paediatric feeding formula, forced ingestion with adverse intent or as a religious ritual, medical prescription of hypertonic saline as an emetic or gargle, accidental ingestion of large quantities of sodium chloride by infants, children, and demented adults, or ingestion of sea water. Partial absorption of hypertonic saline enemas has the same effect. Similarly, severe hypernatraemia develops following the intravenous infusion of hypertonic sodium bicarbonate in the management of severe metabolic acidosis of any cause, including repeated bouts of cardiac arrest, the intrauterine injection of hypertonic saline to induce abortion, and hypertonic haemodialysis (accidental use of dialysate with inordinately high sodium concentration). Assuming reasonably preserved renal function, hypernatraemia caused by hypertonic sodium gain corrects itself swiftly because the prevailing sodium excess is lost in the urine; administration of a loop diuretic and replacement of urine with electrolyte-free water can aid management. Excessively rapid correction of the hypernatraemia should be avoided, especially in asymptomatic patients, as it might reduce the likelihood of full recovery.

Clinical manifestations of hypernatraemia

Signs and symptoms of hypernatraemia largely reflect central nervous system dysfunction and are more prominent when the increase in serum $[\text{Na}^+]$ occurs over a period of hours or is large. In adults, the clinical expression of hypernatraemia can be obscured by a concomitant disease (e.g. cerebrovascular accident) whereas in infants and children signs and symptoms of this disorder are usually evident. Common symptoms in infants include hyperpnoea, muscle weakness, restlessness, a characteristic high-pitched cry, insomnia, lethargy, and even coma. Convulsions are typically absent except in cases of inadvertent sodium loading or aggressive rehydration. Unlike infants, elderly patients generally have few symptoms until the serum sodium exceeds 160 mmol/l. Values greater than 180 mmol/l are associated with a high mortality rate, especially in adults. Intense thirst, present initially, dissipates as the disorder progresses and is absent in patients with hypodipsia. The level of consciousness is correlated with the severity of the hypernatraemia.

Muscle weakness, confusion, and coma are sometimes manifestations of coexisting disorders rather than of the hypernatraemia itself.

Most outpatients with hypernatraemia are either very young or very old. Unlike hypernatraemia in outpatients, hospital-acquired hypernatraemia affects patients of all ages. The clinical manifestations are even more elusive in hospitalized patients who often have pre-existing neurological dysfunction. As in children, rapid sodium loading in adults can cause convulsions and coma. In patients of all ages, orthostatic hypotension and tachycardia reflect marked hypovolaemia.

Hypernatraemia and the attendant hypertonicity elicit water abstraction from the brain resulting in its shrinkage (Fig. 8a and b). The reduction in cerebral volume can cause rupture of blood vessels that bridge the skull and the brain causing cerebral bleeding, subarachnoid haemorrhage, and permanent neurological damage or death. Within hours, however, an adaptive response ensues aimed at restoring brain volume towards baseline and accounts for the gradual improvement of symptomatology. Solute gain by the brain recalls lost water causing brain volume restitution. Electrolyte entry (sodium, potassium, and chloride) within the first few hours is responsible for the initial phase of this adaptation (Fig. 8c), whereas intracellular accumulation of organic solutes (known as idiogenic osmoles or organic osmolytes) completes the process (Fig. 8d). Hypertonicity-induced reduction in cell volume stresses the cytoskeleton, which activates a specific protein kinase; this kinase promotes protein phosphorylation causing activation of transporters that mediate solute uptake by brain cells (Galcheva-Gargova *et al.* 1994). The major brain organic osmolytes include glutamate, glutamine, taurine, and myo-inositol. This adaptation notwithstanding, restitution of brain volume does not correct brain hyperosmolality (Gullans and Verbalis 1993). In fact, this persistent hyperosmolality might induce life-threatening cerebral oedema during corrective hypotonic fluid administration (Fig. 8e).

The mortality rate varies widely according to the severity and the rapidity of onset of hypernatraemia. Separating the contribution to mortality of hypernatraemia itself from that caused by underlying illnesses is a vexing problem.

Management of hypernatraemia

Proper treatment of hypernatraemia requires a two-pronged approach: addressing the underlying cause and repairing the prevailing hypertonicity. Management of the underlying cause includes interruption of gastrointestinal fluid losses; control of pyrexia, hyperglycaemia and glucosuria, withholding lactulose and diuretics, prescription of dDAVP for central diabetes insipidus, correction of hypercalcaemia and hypokalaemia, adjustment of lithium dosage and possible use of amiloride, and correction of the feeding prescription.

In repairing the prevailing hypernatraemia, the clinician must address two questions: (a) what fluid should be administered? (b) At which rate? Depending on the pathogenesis of the hypernatraemia, different correction fluids are required. Inappropriate fluid selection can result in failure to correct the hypernatraemia, aggravation of the disorder, or treatment complications (e.g. pulmonary oedema). Similarly, the rate of fluid therapy must be properly determined to avoid severe adverse effects; overly slow administration of the correct fluid can prolong or even worsen the hypertonic state, whereas an unduly fast fluid therapy can result in cerebral oedema, seizures, permanent neurological damage, and even death.

In patients with acute hypernatraemia (<48 h in duration as seen in accidental sodium loading) rapid correction improves the prognosis

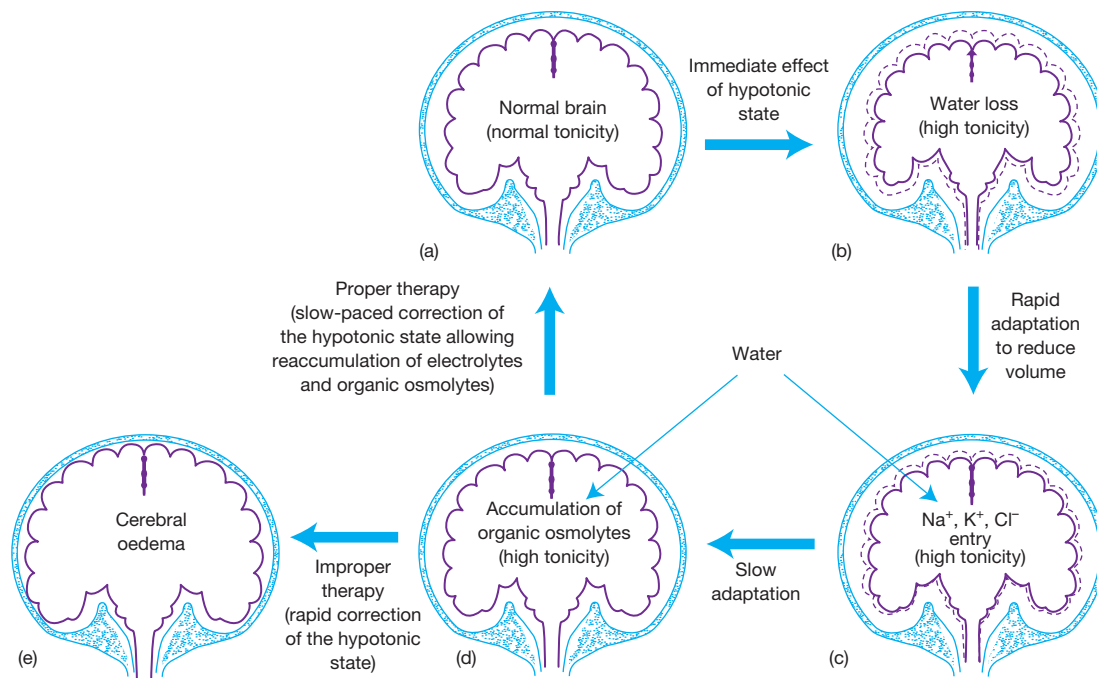


Fig. 8 Effects of hypernatraemia on the brain and adaptive responses. Within minutes after the development of hypertonicity, loss of water from brain cells causes shrinkage of the brain and an increase in osmolality (b). Partial restitution of brain volume occurs within a few hours as electrolytes enter the brain cells (rapid adaptation) (c). The normalization of brain volume is completed within several days as a result of the intracellular accumulation of organic osmolytes (slow adaptation) (d). The high osmolality persists despite the normalization of brain volume. Slow correction of the hypertonic state re-establishes normal brain osmolality without inducing cerebral oedema, as the dissipation of accumulated electrolytes and organic osmolytes keeps pace with water repletion (back to a). In contrast, rapid correction may result in cerebral oedema as water uptake by brain cells outpaces the dissipation of accumulated electrolytes and organic osmolytes. Such overly aggressive therapy carries the risk of serious neurological impairment due to cerebral oedema (e).

without increasing the risk of cerebral oedema, because accumulated electrolytes are rapidly extruded from brain cells. Reduction of the serum sodium by 1 mmol/l/h is appropriate. In patients with hypernatraemia of longer or unknown duration, a slower pace of correction is prudent because the full dissipation of accumulated brain solutes requires several days (Fig. 8). Reduction of serum sodium should thus not exceed 0.5 mmol/l/h to prevent cerebral oedema and convulsions. We recommend a targeted reduction in serum sodium of 10 mmol/l per day for all patients with hypernatraemia except those in whom the disorder has developed over a period of hours, the eventual goal being 145 mmol/l (Adrogué and Madias 2000b). Allowance must be made for ongoing losses of hypotonic fluids, whether obligatory or incidental. 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 or the likelihood of proper gastrointestinal absorption is questionable, fluids should be given intravenously. If the latter is not possible, fluids might be given subcutaneously (hypodermoclysis) (Challiner *et al.* 1994).

Among available fluids, only hypotonic fluids are suitable, including pure water, 5 per cent dextrose, 0.2 per cent sodium chloride ('one-quarter' isotonic saline), and 0.45 per cent sodium chloride (one-half isotonic saline). Their composition and fractional distribution in the ECF compartment are presented in Table 4. The choice of the hypotonic infusate impacts directly on the rate of fluid administration, the more hypotonic the lower the required rate of infusion.

Because the risk of cerebral oedema increases with the volume of infusate, the volume should be restricted to that required to correct hypertonicity. Except in cases of frank circulatory compromise, 0.9 per cent sodium chloride (isotonic saline) is unsuitable for managing hypernatraemia.

After selecting the appropriate fluid, the physician must determine the rate of infusion. The simple formula presented in managing hyponatraemia (Eq. 6) is also applicable in treating hypernatraemia and estimates the change in serum sodium caused by the retention of 1 l of any infusate (Adrogué and Madias 1997). The required volume, and hence the infusion rate, is determined by dividing the change in serum sodium targeted for a given period by the value obtained from the formula. As previously emphasized, because of uncertainties about the effects of infusate as well as ongoing fluid losses, serum $[\text{Na}^+]$ should be checked at frequent intervals during treatment. The following conventional formula for correction of hypernatraemia, should not be used:

$$\text{Water deficit} = \text{TBW} \times \left(\frac{\text{current serum } [\text{Na}^+]}{140} - 1 \right) \quad (8)$$

Although this formula provides an adequate estimate of the water deficit in patients with hypernatraemia caused by pure water loss, it underestimates the deficit in patients with hypotonic fluid loss (Fig. 6c and d). Further, it does not provide information on the differential impact of solutions of variable sodium concentration on the patient's hypernatraemia. For example, depending on whether a hypernatraemic

patient is euvolaemic or hypovolaemic, repair of the disorder requires the administration of free water (i.e. 5 per cent dextrose in water) or sodium-containing solutions (e.g. isotonic saline, half-isotonic saline, or 'one-quarter' isotonic saline), respectively. This shortcoming is avoided by utilizing the recommended formula (Eq. 6). Table 8 depicts illustrative causes of severe hyponatraemia and their management.

Common errors in management

Isotonic saline is unsuitable for correcting hyponatraemia. Consider a 50-year-old man with a serum $[\text{Na}^+]$ of 162 mmol/l and a body weight of 70 kg [estimated volume of total body water, 42 l (0.6×70)]. Retention of 1 l of 0.9 per cent sodium chloride will decrease serum $[\text{Na}^+]$ by only 0.2 mmol/l ($[(154 - 162)/(42 + 1) = -0.2]$). Although the sodium concentration of the infusate is less than the patient's serum $[\text{Na}^+]$, it is not sufficiently low to alter the hyponatraemia substantially. Furthermore, ongoing hypotonic fluid losses might outpace the administration of isotonic saline, aggravating the hyponatraemia. The sole indication for administering isotonic saline to a patient with hyponatraemia is depletion of ECF volume that is sufficient to cause substantial haemodynamic 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 or 0.45 per cent sodium chloride) should be substituted to restore normal haemodynamic values while correcting the hyponatraemia. If a hypotonic fluid is not substituted for isotonic saline, the ECF volume might become seriously overloaded.

Extreme care must be taken to avoid excessively rapid correction or overcorrection of hyponatraemia, with its attendant risk of iatrogenic cerebral oedema. Selecting the most hypotonic infusate that is suitable for the particular type of hyponatraemia ensures the administration of the least amount of fluid. Appropriate allowances for ongoing fluid losses must be made. Most important, the fluid prescription should be reassessed at regular intervals in the light of laboratory values and the patient's clinical status.

Long-term therapy of hyponatraemia

Patients suffering from conditions that predispose to the development of hyponatraemia require implementation of long-term therapy.

Primary hypodipsia Daily determination of body weight can help early detection of hypodipsia-induced dehydration in the elderly. In addition, adherence to a daily fluid-intake schedule promotes prevention and management of hyponatraemia in primary hypodipsia. Risk factors for dehydration include age more than 85 years, female gender, bedridden status, laxative use, chronic infections, more than four chronic disorders, and intake of more than four medications (Lavizzo-Mourrey *et al.* 1988). Consideration of the risk factors present in a given patient should aid prescription and implementation of measures against dehydration. In case of associated defect in vasopressin secretion, specific management is required.

Central diabetes insipidus Most patients with CDI have a normal or only mildly elevated serum sodium because of concurrent stimulation of thirst. They develop hyponatraemia only if thirst or access to water is impaired. Management aims primarily at the control of polyuria by hormone replacement therapy. The vasopressin analogue, desmopressin (also known as dDAVP, 1-desamino-8-D-arginine vasopressin) is usually administered as an intranasal spray once or twice a day (dose range, 5–20 μg) (Richardson and Robinson 1985). Desmopressin is also available as a tablet for oral intake with the daily maintenance

dose ranging from 0.1 to 0.8 mg in divided doses. Water retention and development of hyponatraemia is an important potential risk to the use of desmopressin in CDI. Consequently, the minimum dose of the drug that is sufficient to control polyuria should be prescribed in association with continued patient education about water balance.

An additional tool to reduce urine output (i.e. from several litres per day in partial CDI or severe nephrogenic diabetes insipidus, and 10–15 l per day in severe CDI) is to restrict salt and protein intake. If, for example, the patient's maximal urine osmolality is 150 mOsm/kg H_2O and the daily obligatory solute load is reduced to 450 mmol/day, then the daily urine output reaches 3 l/day ($450/150 = 3$).

Less expensive non-hormonal drugs can be used to control polyuria in CDI, including chlorpropamide, carbamazepine, clofibrate, thiazide diuretics, or non-steroidal anti-inflammatory drugs (NSAIDs). Chlorpropamide, an oral hypoglycaemic agent, has been widely used to enhance the renal response to ADH or desmopressin and to stimulate ADH release. Carbamazepine, an antiseizure agent, increases the response to ADH, and clofibrate (lipid-lowering drug) increases ADH release. The above three drugs can reduce urine output by as much as 50 per cent. Hydrochlorothiazide and NSAID can limit polyuria independent of ADH and are therefore used either in CDI or nephrogenic diabetes insipidus.

Nephrogenic diabetes insipidus A mild form of nephrogenic diabetes insipidus is relatively common in elderly patients or those who have a renal disease that decreases modestly the maximum concentrating capacity. Nocturia develops but is generally not severe enough to result in polyuria. Conversely, symptomatic polyuria due to nephrogenic diabetes insipidus is most frequently the result of hypercalcaemia or chronic lithium use in adults or of an X-linked hereditary nephrogenic diabetes insipidus in children.

Therapy of symptomatic nephrogenic diabetes insipidus is primarily aimed at the correction of the underlying disorder whenever possible, or at the discontinuation of the toxic drug. Correction of hypercalcaemia usually improves or fully reverses the renal dysfunction; discontinuation of lithium therapy can eradicate or ameliorate lithium-induced nephrogenic diabetes insipidus. Lithium administration can increase plasma parathyroid hormone and rarely cause hypercalcaemia, which, in turn, exacerbates the lithium-induced urine concentrating defect.

If lithium therapy must continue, the concurrent administration of amiloride, a potassium-sparing diuretic, might improve mild to moderate urinary concentrating defects. Amiloride closes sodium channels in collecting tubule cells and reduces renal lithium accumulation. This measure is ineffective in patients with severe urinary concentrating defects. Amiloride therapy can cause volume depletion with an attendant increase in proximal lithium reabsorption requiring a reduction in daily lithium dosage.

If the underlying disease cannot be corrected, a number of generic measures can be applied to patients with nephrogenic diabetes insipidus to limit urine output. They include a decreased solute load (i.e. adherence to a low-sodium chloride and low-protein diet), diuretics, and NSAIDs. Diuretic agents, mostly thiazides, such as hydrochlorothiazide, 25 mg once or twice daily, coupled with a low-sodium chloride intake can reduce urine volume by about 50 per cent. They induce mild volume depletion, which in turn increases proximal fluid reabsorption and limits water delivery to the collecting tubule. A combination of thiazide and amiloride potentiates the overall effect and has the additional advantage of reducing thiazide-induced potassium losses. A loop diuretic might help diabetes insipidus by decreasing sodium chloride transport in the

Table 8 Managing severe hypernatraemia: illustrative cases

Case no.	Time (h)	Data	Diagnosis/treatment plan	Fluid prescription
1	0	80-year-old man with severe obtundation, fever, and tachypnoea; decreased skin turgor; dry mucous membranes, supine BP 137/80 mmHg without orthostatic changes; weight 64 kg [Na ⁺] 166 mmol/l, [K ⁺] 4.0 mmol/l, Sosm 345 mOsm/kg H ₂ O	Hypernatraemia due to unreplaced water losses 5% dextrose to reduce [Na ⁺] by 10 mmol/l over 24 h	TBW, $0.5 \times 64 = 32$ l $\Delta[\text{Na}^+] = \frac{0 - 166}{32 + 1} = 5.0$ mmol/l per 1 l infusate For a goal of $\Delta[\text{Na}^+] 10$ mmol/l/24 h, $10/5 = 2$ l/24 h are required Adding 1.5 l to compensate for ongoing, obligatory water losses over the 24 h period $2 + 1.5 = 3.5$ l/24 h are required or 146 ml/h
	6	Mental status unchanged; haemodynamically stable [Na ⁺] 164 mmol/l	Treatment plan unchanged Close monitoring	Continue present infusate at 146 ml/h
	12	Moderate obtundation haemodynamically stable. [Na ⁺] 160 mmol/l, glucose 110 mg/dl, Sosm 335 mOsm/kg H ₂ O	Treatment plan unchanged Watch for hyperglycaemia Close monitoring	Continue present infusate at 146 ml/h
2	0	48-year-old woman with bout of gastroenteritis, who presents with fever and moderate obtundation; decreased skin turgor, supine BP 110/70 mm; standing BP 100/65 mmHg; weight 60 kg [Na ⁺] 156 mmol/l, [K ⁺] 3.0 mmol/l, [HCO ₃ ⁻] 28 mmol/l Sosm 325 mOsm/kg H ₂ O	Hypernatraemia due to hypotonic fluid losses; potassium depletion. Volume repletion, potassium repletion, 0.45% NaCl containing 20 mmol of KCl per litre to decrease [Na ⁺] by 10 mmol/l over 24 h	TBW, $0.5 \times 60 = 30$ l $\Delta[\text{Na}^+] = \frac{(77 + 20) - 156}{30 + 1} = 1.9$ mmol/l per 1 l infusate For a goal of $\Delta[\text{Na}^+] 10$ mmol/l/24 h $10/1.9 = 5.3$ l/24 h are required Adding 2 l to compensate for ongoing fluid losses over the 24 h period, $5.3 + 2 = 7.3$ l/24 h are required or $\cong 300$ ml/h
	8	Mild obtundation, haemodynamically stable. [Na ⁺] 154 mmol/l, [K ⁺] 3.2 mmol/l	Unsatisfactory pace of correction Switch infusate to 0.2% NaCl containing 20 mmol of KCl per litre to decrease [Na ⁺] by 6 mmol/l over 12 h	$\Delta[\text{Na}^+] = \frac{(34 + 20) - 154}{30 + 1} = -3.2$ mmol/l per 1 l infusate For a goal of $\Delta[\text{Na}^+] 6$ mmol/l/12 h $6/3.2 = 1.9$ l/24 h are required Adding 1 l to compensate for ongoing fluid losses over the 12 h period, $1.9 + 1 = 2.9$ l/12 h are required or $\cong 240$ ml/h
	20	Mildly somnolent, haemodynamically stable. [Na ⁺] 149 mmol/l, [K ⁺] 3.4 mmol/l	Pace of correction satisfactory	Continue present infusate at 240 ml/h

thick ascending limb of the loop of Henle. Because renal prostaglandins antagonize the action of ADH, inhibition of their renal synthesis by NSAIDs (e.g. indomethacin) can help control polyuria. Combination of NSAID and a thiazide diuretic can be used for increased effectiveness. Finally, exogenous vasopressin (i.e. dDAVP) can be of benefit in patients with inadequate response to other therapeutic agents; in fact, most patients with nephrogenic diabetes insipidus do not have complete resistance to vasopressin.

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