



Clinical approach to disorders of salt and water balance

Emphasis on integrative physiology

Mitchell L. Halperin, MD, FRCPC^{a,*},
Desmond Bohn, MB, FRCPC^b

^a*Division of Nephrology, St. Michael's Hospital and the University of Toronto, St. Michael's Hospital Annex, 38 Shuter Street, Toronto, Ontario, M5B 1A6, Canada*

^b*Department of Critical Care Medicine of the Hospital for Sick Children, and the Department of Anaesthesia, The University of Toronto, 555 University Ave., Toronto, Ontario, M5G 1X8 Canada*

With our current emphasis on subspecialty medicine, consultants suggest possible diagnoses and treatments for patients who have abnormalities within their areas of expertise. The medical team responsible for the care of that patient must integrate these suggestions into an overall management plan. Therefore, teamwork is especially important for the care of a patient.

The underlying basis for a given disorder may be revealed when an integrative analysis is performed. Some defects may only become evident during therapy. These challenges are especially important for problems in fluid and electrolyte balance in an intensive care unit (ICU) setting because they may become life-threatening very rapidly. How to anticipate and avoid these dangers is illustrated in the context of case examples selected for presentation in this article.

There are two different, but not mutually exclusive, ways to arrive at a clinical diagnosis and to design its therapy when the problem is in the salt and water area. The more traditional approach begins with data from the history, physical examination, and laboratory tests. This information is used to generate a list of possible causes of the disorder. Our approach differs in that it begins with the application of simple principles of physiology at the bedside (Table 1) [5]. It relies on deductive reasoning and a quantitative analysis. The starting point is defined by the consulting service—what they believe to be most critical for their patient.

* Corresponding author.

E-mail addresses: mitchell.halperin@utoronto.ca (M.L. Halperin), dbohn@sickkids.ca (D. Bohn).

Table 1
Physiologic principles used at the bedside

Physiologic principle	Use at the bedside
Polyuria	Divide polyuria into:
Urine volume = Osm/UOsm	Osmotic diuresis if > 1000 mOsm/d
	Organic solutes
	Examine filtered load
	Seek metabolic origin (e.g., urea)
	Electrolytes (were they infused?)
	Water diuresis ($U_{osm} < P_{osm}$)
	$UOsm \propto osm$ excretion and flow rate
Impact of a change in P_{Na}	Main threat is change in brain ICF volume
P_{Na} inversely related to ICF volume	Na^+ content reflects the ECF volume
Hypernatremia	Basis revealed by tonicity balance
Caused by Na^+ gain or water deficit	Identify cause for the release of vasopressin
Calcium receptor in the loop of Henle	$NaCl$, K^+ wasting and concentrating defect
Creates furosemide-like effect	Can be induced by cations (gentamicin)
Catabolic state	Confirmed by urea (572 mmol/100 g protein)
Protein oxidation causes urea appearance	Therapy with exogenous protein \pm anabolics
Hyponatremia	Ask if acute (<48 h) = increased brain ICF volume
Find source of EFW and vasopressin	Risk factors = young age, women, increased ECF volume
Calculate new ICF volume	Urgent therapy 3% saline
Calculate ECF Na^+ content	Retained lavage fluid = different
Assess possible K^+ deficiency	Most are chronic (danger is ODS)
	Seek reason for vasopressin, especially if a reversible cause might be present
	Treat slowly (<9 mmol/L/d); slower if K^+ deficit or malnourished

Abbreviations: U=urine; P=plasma.

To make this article interactive, we pause periodically and ask the reader "questions to consider" prior to providing our discussion of that issue. In each case, there is an abnormal plasma sodium (Na^+) concentration (P_{Na}) in an ICU setting.

Polyuria and hypernatremia

Illustrative case 1

Polyuria (current urine flow rate 10 ml/min) developed suddenly in a 14-year-old boy (weight 50 kg, total body water 30 liters) during resection of a craniopharyngeoma. His P_{Na} rose from 140 to 155 mmol/ over 6 hours. He was given 3 liters of isotonic saline intravenously and his urine output was 4 liters. He had also received an infusion of mannitol. The aim of the consult was to define goals of therapy for this patient.

Initial quantitative analysis

The urine flow rate of 10 ml/min, if extrapolated over 24 hours, is equivalent to 14.4 liters per day. This volume exceeds the patient's extracellular fluid (ECF) volume and is virtually equal to half of total body water. Faced with this medical emergency, we ask the reader: "What was responsible for this massive polyuria?"

What was responsible for this massive polyuria?

Physiology principle 1. The urine flow rate is a function of two factors (Eq. 1). Hence polyuria has two causes, a larger than normal solute excretion rate (osmotic diuresis) and/or an inability to raise the concentration of solutes in the urine appropriately (water diuresis). In an osmotic diuresis, each liter of urine contains at least 300 milliosmoles of the causative solute (and other solutes as well) [32].

Urine flow rate (liters/day)

$$= \text{Number of Solutes excreted} / [\text{Solute}]_{\text{urine}} \quad (1)$$

Return to the bedside. Using the values from surgery, 3 milliosmoles of extra solutes (10 ml/min \times a minimum of 300 milliosmoles/l in an osmotic diuresis) would need to be excreted each minute if this was a glucose, urea, or mannitol-induced osmotic diuresis. This would require the presence of very high concentrations of these organic solutes in plasma if one of them caused the polyuria. If the urine composition were not available, the following calculation could be performed to determine whether enough solutes were filtered to cause the osmotic diuresis. With a normal glomerular filtration rate (GFR), the concentration of glucose in the filtrate would have to be 27 mmol/l (486 mg/dl) higher than the renal threshold of 10 mmol/l (180 mg/dl) to filter 3 mmol of glucose per min to permit it to cause this degree of osmotic diuresis (24 mmol/l \times 0.125 l/min). Hence the blood sugar levels would need to be 666 mg/dl (37 mmol/l) for this to be a glucose-induced osmotic diuresis [14]. If urea were the principal urine osmole, its concentration in plasma would have to be close to 60 mmol/l (BUN 168 mg/dl) because close to half of the filtered urea is normally reabsorbed [9]. Even higher plasma concentrations would be needed if the GFR were lower than 125 ml/min. For mannitol, at least 50 g (\sim 290 mmol) would have to be infused for every liter of urine excreted.

Based on this, extra information was sought. Because the blood sugar and BUN were both in the normal range and the quantity of mannitol infused was too small, an osmotic diuresis due to organic solutes was ruled out. The fact that the urine Na^+ + potassium (K^+) concentration was only 50 mmol/l ruled out a saline-induced osmotic diuresis. Therefore the basis for the polyuria was a water diuresis, a diagnosis that was confirmed when his urine osmolality was known (120 mOsm/kg H_2O).

The next question is, "What was the cause of the large water diuresis?" It is essential to recall that his P_{Na} was 155 mmol/l during the polyuria.

What was the cause of the large water diuresis?

Physiology principle 2. The control system for water has its sensor (specialized area of the hypothalamus) in a different location from one of its response elements (excretion of water by the kidney). Therefore a messenger (vasopressin) must communicate between these two locations (Fig. 1). The cell volume of the central osmostat shrinks sufficiently when the P_{Na} exceeds 140 mmol/l and this leads to an augmented release of vasopressin. Vasopressin causes the distal segments of the nephron to become permeable to water due to the insertion of water channels [27], causing the urine to become maximally concentrated (the urine osmolality should be 3–4-fold higher than the plasma osmolality) [29].

Return to the bedside. A lesion releasing vasopressinase was unlikely in this patient. There were two factors suggesting that the likely diagnosis was central diabetes insipidus (DI). First, there was the neurosurgery and a disease process (craniopharyngeoma) that could have compromised the ability to release vasopressin from the hypothalamus. Second, there was a large water diuresis (the urine osmolality was 120 mOsm/kg H_2O) despite the presence of a stimulus for the release of vasopressin (hypermnatremia). To confirm that the DI was central rather than nephrogenic in origin, vasopressin was administered. Bearing in mind that vasopressin acts in a matter of minutes [27], we ask the reader, "How low should the urine flow rate be when vasopressin acts?" The measured value for this urine flow rate was 6 ml/min.

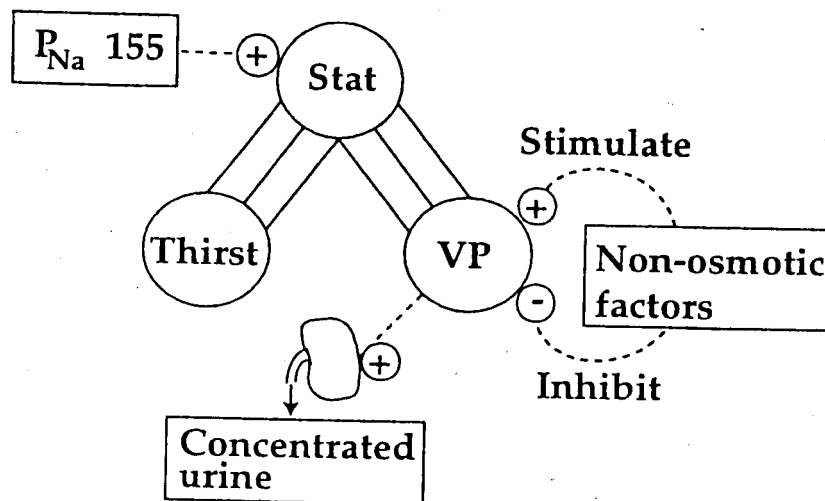


Fig. 1. Control system for water excretion. The circles represent structures in the hypothalamus. The tonicity stat (osmostat) detects a change in the P_{Na} . Because of hypernatremia (box on the left), this center leads to the release of vasopressin (VP). Vasopressin acts on the distal nephron to cause it to become permeable to water leading to the excretion of concentrated urine. There are also non-osmotic stimuli that influence the release of vasopressin.

How low should the urine flow rate be when vasopressin acts?

Application of physiology principle 1. First, the urine flow rate depends on two factors, the number of impermeable solutes (effective or non-urea osmoles) in the lumen of the terminal collecting duct and the effective osmolality (non-urea osmolality) of the papillary medullary interstitium (Eq. 1) [11]. Second, a typical diet leads to the excretion of 800 mosmoles/day, with half being urea and the other half, electrolytes. Third, because the non-urea osmolality can rise to 600 mOsm/kg H₂O when vasopressin acts, the expected urine flow rate is close to 0.67 ml/min under these conditions (400 mosmoles of electrolytes excreted at a concentration of 600 mosmoles per liter). Fourth, the maximum total and effective osmolalities in the renal interstitial compartment decline during a prior water diuresis and it takes time to reconstitute this environment after vasopressin acts.

Return to the bedside. A urine osmolality of 120 mOsm/kg H₂O is not the expected value during a water diuresis when the urine flow rate is 10 ml/min. Rather, the urine osmolality should have been 50–60 mOsm/kg H₂O if 800 milliosmoles were excreted in 1440 min (0.5–0.6 milliosmoles/min) [5]. Moreover, in a water diuresis, water is largely impermeable in the distal nephron. Therefore a high rate of excretion of osmoles should not influence the urine flow rate when there is a lack of vasopressin. In contrast, when vasopressin acts, the osmole excretion rate will exert a major effect on the urine flow rate (Eq. 1).

A change in urine flow rate is obvious at the bedside whereas a delay is expected before the laboratory reports the urine osmolality. Therefore clinical decision making will be based initially on the decline in urine flow rate. On the one hand, normal subjects have a minimum urine flow rate of close to 0.5 ml/min when vasopressin acts [30]. Accordingly, one might anticipate that the urine volume should fall to 0.5 ml/min after vasopressin was given. A surprise is in store if this were the logic used. The error would be to rely on data obtained from one setting (normal subjects) and apply them to this patient in the ICU.

Comment. Had a physiologic analysis been performed at the time when the urine flow rate was 10 ml/min, the observed decrease to 6 ml/min after vasopressin administration could have been anticipated if three facts were taken into account. First, the patient was excreting effective osmoles (urine electrolytes) at a rate that was close to 3-fold that of subjects consuming a typical Western diet (10 ml/min × 50 mmol Na⁺ + K⁺ /l = 0.5 mmol/min) vs. the expected 225 mmol Na⁺ + K⁺ /day or 0.15 mmol/min. Second, the huge water diuresis that occurred prior to the administration of vasopressin should diminish the medullary interstitial osmolality and this would take time to be reconstituted. Thus the maximum urine osmolality would be similarly reduced. Third, the peak natriuresis might not have been reached at the time that the first urine osmolality was measured. Indeed, the rate of osmole (Na⁺ + K⁺) excretion continued to rise after vasopressin was given. Thus a urine flow rate after vasopressin that was more than 10-fold that of subjects consuming a typical Western diet was a more realistic expectation. Hence, by not applying physiologic principles to the bedside, a series of compounding errors were set into motion that had grave consequences for the patient. One of the errors was to give multiple doses of a long-acting preparation of vasopressin,

dDAVP. The grave consequences of this error in therapy will be discussed in the response to the question, *what was the "occult" threat to survival?*

Now we ask the reader to consider, *"What is the basis of hypernatremia in this patient with central DI?"*

What is the basis of hypernatremia in this patient with central DI?

Physiology principle 3. To raise the P_{Na} by 10%, there must either be a gain of Na^+ and/or a deficit of water in the ECF compartment (Table 1). In quantitative terms, the gain of Na^+ is calculated in total body water terms so a rise in P_{Na} of 15 mmol/l requires a positive balance of approximately 450 mmoles of Na^+ (15 mmol/l \times 30 liters total body water (i.e., 60% of body weight in this patient). On the other hand, because water distributes across all body fluid compartments in proportion to their volumes [33], the deficit of water must be close to 10% of total body water (10% \times 30 liters, or 3 liters) to cause the observed 10% rise in P_{Na} .

Return to the bedside. We begin with an analysis based on electrolyte-free water (water without Na^+ + K^+) to illustrate its limitations (Fig. 2). To think in electrolyte-free water terms [10,23,28], an imaginary calculation is performed where the 4 liters of urine in our patient are divided into 1.3 liters of isotonic saline (use 150 mmol of Na^+ + K^+ /liter for simplicity) and the remaining 2.7 liters is called electrolyte-free water (Fig. 2). It is important to calculate an electrolyte-free water balance rather than focus on either excretion or input to determine why the P_{Na} changed. This can easily be done in our patient because the input contained 0 liters of electrolyte-free water while 2.7 liters of electrolyte-free water were excreted. This negative balance of 2.7 liters of electrolyte-free water should raise the P_{Na} by close to 15 mmol/l (140 mmol/l \times (30/27.3 liters). If an electrolyte-free water balance were used to design therapy, a positive balance of

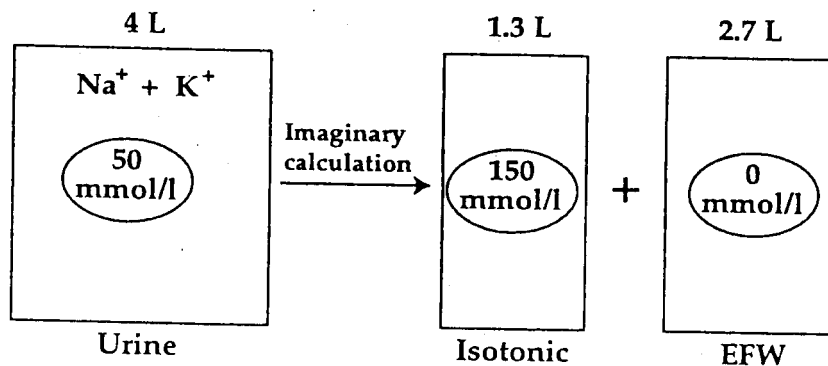


Fig. 2. Calculation of electrolyte-free water. The urine volume in Case 1 was 4 liters (large rectangle) and its Na^+ + K^+ concentration was 50 mmol/l (left of arrow). This solution can be divided into two imaginary components, 1.3 liters of isotonic saline (150 mmol Na^+ + K^+ /liter) and 2.7 liters of electrolyte-free water (EFW). (From RossMark Medical Publishers, *The Acid Truth and Basic Facts*, 4th ed, 1997; with permission) [13].

2.7 liters of electrolyte-free water should be induced to correct the hypernatremia. Notwithstanding, there are many ways to achieve a negative balance of 2.7 liters of electrolyte-free water [3]. For example, if we made a change only to the volume of isotonic saline infused during the period in which hypernatremia developed (now 4 liters instead of 3 liters), there is still no electrolyte-free water administered so the balance for electrolyte-free water is still minus 2.7 liters. Therefore the rise in P_{Na} would be identical, but its basis would be different (Table 2). Obviously, the goals of therapy should also be different in these examples despite the fact that the negative balance of electrolyte-free water and rise in P_{Na} were identical. Therefore one cannot rely on an electrolyte-free water balance to guide therapy (Table 2). [3].

A better way to determine why the P_{Na} changed is to calculate a tonicity balance (Fig. 3) where all inputs and outputs are also divided into two components, total volume of water and $Na^+ + K^+$ —each of which is analyzed separately [3]. Mass balance for Na^+ plus K^+ rather than just Na^+ must be included because Na^+ may enter cells in conjunction with the exit of K^+ [8]. Thus the loss of K^+ with chloride (Cl^-) or bicarbonate can be thought of as a loss of their Na^+ salts from the ECF compartment. When considering $Na^+ + K^+$ in isolation, for every mmol retained per liter of total body water, the rise in P_{Na} will be 1 mmol/l [33]. Similarly, a gain of 1 liter of water, when considered in isolation should lower the P_{Na} by the formula: $P_{Na} \times (1/\text{total body water})$.

In addition to predicting the rise in P_{Na} [3], the tonicity balance also provides reliable information about its cause (Table 2). In our patient, the volume of water infused was 1 liter less than the urine volume. Recall that 3 liters of net water loss would be required to raise the P_{Na} by 10%. Therefore hypernatremia in our patient was not due solely to a water deficit despite the large electrolyte-free water diuresis. Since the patient was given 450 mmol Na^+ and excreted 200 mmol Na^+ ($+ K^+$) in his urine, there was a net gain of 250 mmol of $Na^+ + K^+$. The

Table 2
Hypernatremia and a negative balance of 2.7 L of electrolyte-free water^a

	$Na^+ + K^+$ (mmol)	Water (L)	EFW (L)	Therapy from balances		
				EFW	Tonicity	
Case 1						
Input	450	3	0			
Output	200	4	2.7			
Balance	+250	-1	-2.7	+2.7 L H ₂ O	+1 L H ₂ O	-250 mmol Na ⁺
Change IV to 4L of isotonic saline						
Input	600	4	0			
Output	200	4	2.7			
Balance	+400	0	-2.7	+2.7 L H ₂ O	0 L H ₂ O	-400 mmol Na ⁺

^a The P_{Na} rose from 140 to 155 mmol/L in each setting. The only difference is the volume of isotonic saline infused over the time period of observation. In both settings, there is a negative balance of 2.7 liters of electrolyte-free water (EFW). The goals of therapy to correct the hypernatremia were clear only after a tonicity balance was calculated.

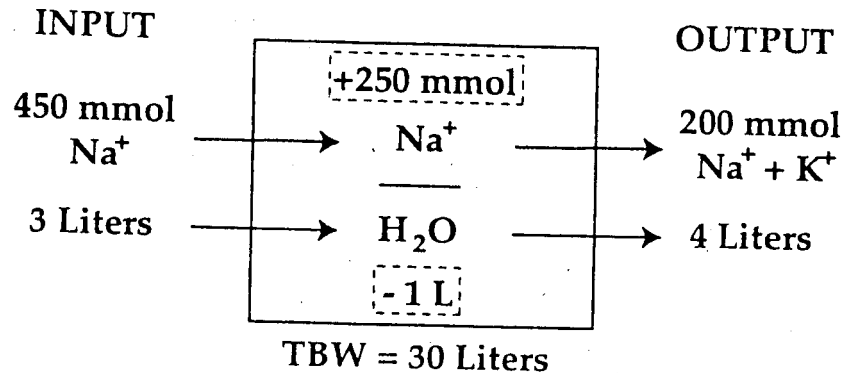


Fig. 3. Calculation of a tonicity balance. The rectangle represents the body with its concentration of Na^+ . The input of $\text{Na}^+ + \text{K}^+$ and of water are shown on the left; the output of $\text{Na}^+ + \text{K}^+$ and of water are shown on the right of this rectangle in Case 1. Balances are shown in dashed boxes inside the rectangle.

combination of a deficit of 1 liter of water and a gain of 250 mmol of Na^+ would explain the rise in P_{Na} . In contrast to information provided by an electrolyte-free water balance, the tonicity balance revealed the goals for therapy—create a negative balance of 250 mmol of $\text{Na}^+ (+ \text{K}^+)$ along with a positive balance of 1 liter of water (Table 2). This therapy will correct hypernatremia and return both the ICF and ECF compartment volumes to normal. Moreover, the tonicity balance provides a physiologic basis for the clinical implications of hypernatremia. When a tonicity balance is used in the hypothetical example (i.e., when 4 liters of isotonic saline were administered), it is clear that the goals of therapy are to create a negative balance for $\text{Na}^+ + \text{K}^+$ of 400 mmol and a nil balance of water. Given the short time interval, insensible losses would be relatively small. Therefore, because of the absence of fever, we would not include them in this patient.

Clinical course. After administration of vasopressin, the measured concentrations of $\text{Na}^+ + \text{K}^+$ in the urine rose to 175 mmol/l. The intravenous fluid therapy was half-isotonic saline (close to 75 mmol Na^+ /liter) at volumes equal to the urine output—this caused a deficit of almost 100 mmol of Na^+ per liter of throughput. After the excretion of 2.5 liters of urine, the desired negative balance of 250 mmol of Na^+ would have occurred. The other goal of therapy was to expand his body water by 1 liter and this was achieved by giving a positive balance of 1 liter of electrolyte-free water (i.e., 1 liter of D_5W if hyperglycemia was not present). At this point, both his ICF and ECF volumes and composition would be restored to normal (P_{Na} would be 140 mmol/l). A successful clinical outcome was anticipated. We ask the reader, “*What is the “occult” threat to survival?*”

What was the “occult” threat to survival?

Application of physiology principle 3. The P_{Na} is used to reflect the volume of the ICF compartment for three reasons (Fig. 4). First, water crosses cell

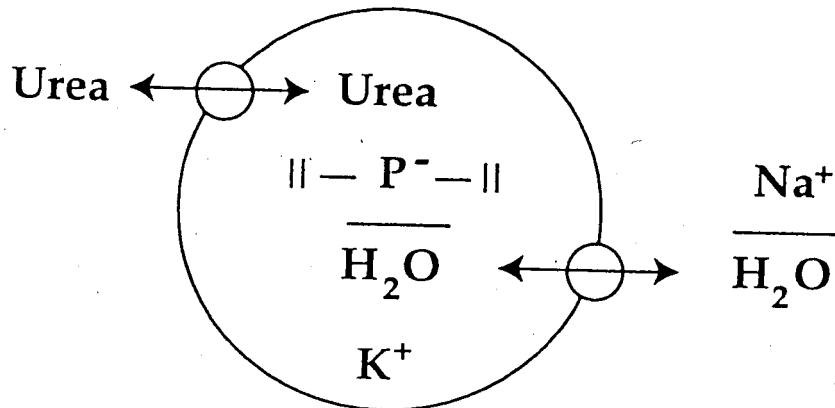


Fig. 4. P_{Na} Concentration reflects the ICF volume in the absence of hyperglycemia and mannitol infusion. The circle represents the ICF compartment that contains macromolecular anions (P^-) and its major effective osmole, the cation K^+ . Urea, shown on the left, is not an effective osmole because it virtually always has an equal concentration in the ECF and ICF compartments. The osmoles restricted to the ECF compartment are Na^+ and its attendant anions. Osmotic equilibrium is achieved because water can cross this cell membrane rapidly.

membranes rapidly to achieve osmotic equilibrium. Second, the number of “effective osmoles” (osmoles other than urea) in the ICF compartment remains constant in most acute settings. Third, in the absence of hyperglycemia and/or mannitol accumulation in the ECF compartment, the effective ECF osmoles are Na^+ and its attendant anions, Cl^- and bicarbonate. Therefore when hypernatremia develops, the volume of cells will be smaller unless there was a gain in ICF osmoles in muscle for example due to a recent seizure [36] or rhabdomyolysis [15].

The “target organ” of clinical importance is the brain because it is in a confined rigid space and it cannot gain intracellular particles in an acute setting. The main danger in this setting is an intracerebral hemorrhage. In contrast, hyponatremia usually implies that its ICF volume is expanded and ultimately may lead to cerebral herniation because of the rigidity of the skull and the fact that close to 67% of total brain water is in its ICF compartment.

Return to the bedside. Once the P_{Na} has returned to 140 mmol/l, progressive acute hyponatremia from ongoing negative Na^+ balance is a real danger unless therapy is modified quickly. One can anticipate that the urine Na^+ concentration may be almost as high as the medullary interstitial $Na^+ + K^+$ concentration when vasopressin acts because of the low urea concentration in the renal medullary interstitium (the result of the low urine urea concentration). Because a long-acting (~ 10 h) form of vasopressin (dDAVP) was given and the vast majority of urine osmoles were $Na^+ + K^+$ salts, it is not surprising that the urine Na^+ concentration rose to 300 mmol/l (Fig. 5). Therefore it is easy to anticipate why hyponatremia would develop during therapy to correct hypernatremia because half-isotonic saline (75 mmol Na^+ /l) was given at a rate equal to urine

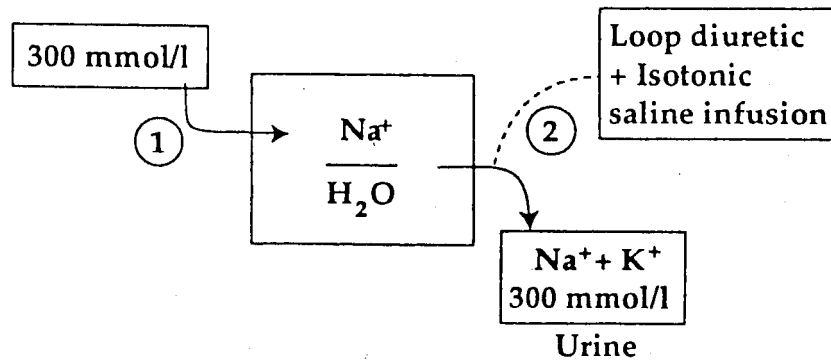


Fig. 5. Options of therapy to prevent the development of hyponatremia. The actions of vasopressin led to the urinary excretion of 1 liter of hypertonic saline (300 mmol/l) in Case 1. To avoid the development of hyponatremia, the intravenous infusion and urine output must have the same concentrations of Na^+ (+ K^+) and the same volume. Thus either the concentration of saline infused must be 300 mmol/l or the urine must be adjusted so that it becomes close to isotonic saline (give a loop diuretic). (From RossMark Medical Publishers, *The Acid Truth and Basic Facts*, 4th ed, 1997; with permission.)

output. Because this strategy was not changed when the P_{Na} fell to 140 mmol/l, the patient became progressively hyponatremic and died due to brain swelling that led to herniation. We ask the reader, "How could this fatal outcome be avoided?"

How could this fatal outcome be avoided?

Application of physiology principle 3. To prevent a change in the P_{Na} , the input must be identical to the output both in terms of volume and electrolyte content (Fig. 5).

Return to the bedside. There are two ways to achieve a tonicity balance (Fig. 5). First, one could infuse saline at the same concentration and flow rate as in the urine; second, one could administer a loop diuretic to lower urine Na^+ + K^+ concentration to approximate that of plasma. With this latter strategy, giving isotonic saline at the same rate as the urine output could have replaced all renal losses other than K^+ while preventing a fall in the P_{Na} . At any point before the tragic end, his P_{Na} could have been raised to a non-threatening level easily by the administration of 1 mmol Na^+ (without water) per liter of total body water times the desired change in the P_{Na} . Raising his P_{Na} from 125 mmol/l to 130 mmol/l would have required a positive balance of 150 mmol of Na^+ ($5 \text{ mmol/l} \times 30 \text{ liters}$) which could have been accomplished by the rapid infusion of close to 0.3 liters of 3% NaCl. It is important to recognize that a reasonably rapid rate of correction of hyponatremia is not a risk factor for osmotic demyelination in a patient with acute hyponatremia [31].

Concluding remarks for case 1

Using simple whole body physiology (Table 1), deductive reasoning, and a quantitative analysis emphasizing mass balance, the basis of the polyuria was

clearly a water diuresis due to central DI. By calculating the osmole excretion rate and deducing that there was an excessive excretion of electrolytes, it was important to predict that the urine flow rate might only decline to around 6 ml/min after vasopressin was given. Armed with these insights, the patient would not have been given so large a dose of this hormone. For therapy, the objectives were also clear—return the body compartment volumes and composition to normal. Using a tonicity balance, the basis of hyponatremia was a positive balance of 250 mmol of Na^+ (and Cl^-) and a deficit of 1 liter of water. Accordingly, the design of therapy was to create a negative balance for Na^+ (250 mmol) while increasing water balance by 1 liter. Moreover, the dangers in this setting could be anticipated. Once the P_{Na} returned to normal, one must maintain Na^+ and water balances. Because the urine Na^+ concentration was high and the urine flow rate was also large, intravenous solutions should be given at the same rate as the urine output while ensuring that their overall Na^+ concentration was equal to that of the urine (Fig. 5).

Perhaps the simple take-home message is that a physiological approach should be the one used at the bedside in the ICU. There are two other points that merit emphasis. First, from a practical and safety perspective, it is critical to monitor the P_{Na} closely during and after therapy to be sure the goals of therapy are indeed being achieved. Second, because hyponatremia developed so acutely, it should not be dangerous to return the P_{Na} to normal over a period of one day.

Illustrative case 2

Three problems prompted the transfer of a 70-kg male to the ICU following a recent bone marrow transplant. First, he was heavily immunosuppressed and developed an acute respiratory tract infection for which he was treated with antibiotics including gentamicin. Second, he became hypotensive (blood pressure nadir was 65/40 mm Hg) yet he developed non-oliguric acute renal failure (plasma creatinine rose from 0.9 to 4.6 mg/dl (100 to 412 $\mu\text{mol/l}$), BUN rose from 14 to 213 mg/dl, urea 5 to 76 mmol/l). Third, his P_{Na} rose from 140 to 157 mmol/l over several days in the ICU. Balance data were available for the day his P_{Na} rose from 147 to 155 mmol/l. They revealed a positive balance of both 1 liter of water and 378 mmol $\text{Na}^+ + \text{K}^+$ (7 liters of hypotonic saline ($\text{Na}^+ + \text{K}^+$ of 90 mmol/l) were infused and he excreted 6 liters of urine ($\text{Na}^+ + \text{K}^+$ concentration of 42 mmol/l) (Fig. 6). His urine osmolality was 524 mOsm/kg H_2O .

At this point, we ask the reader to consider the following questions. “*What was the basis of the polyuria and hyponatremia?*” “*Why was the urine $\text{Na}^+ + \text{K}^+$ concentration so low?*”

What was the basis of the polyuria?

Physiology principle 4. Function of the thick ascending limb of the loop of Henle (TAL) is needed to concentrate the urine and for conservation of Na^+ and Cl^- by the kidney. These cells have a calcium receptor on their basolateral aspect (facing the blood side, Fig. 7). When this receptor is occupied by a

