Clinical Laboratory Evaluation of the Syndrome of Inappropriate Secretion of Antidiuretic Hormone

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Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a frequent cause of hypotonicity. Although the differential diagnosis with other causes of hypotonicity such as salt depletion is sometimes challenging, some simple and readily available biologic parameters can be helpful in the diagnosis of SIADH. In SIADH, urea is typically low; this is less specific for elderly patients, for whom lower clearance of urea accounts for higher values. Low levels of uric acid are more often seen in SIADH (70%) compared with salt-depleted patients (40%). Typically, patients with SIADH will show a lower anion gap with nearly normal total CO_2 and serum potassium, this despite dilution. In patients with hyponatremia secondary to hypocorticism, total CO_2 is usually lower than in nonendocrine SIADH despite low urea and uric acid levels. Urine biology can also be helpful in diagnosis of SIADH because patients with SIADH have high urine sodium (Na; >30 mEq/L), and most of them will have a high fractional excretion of Na (>0.5% in 70% of cases), reflecting salt intake. Conversely, low urine Na in patients with SIADH and poor alimentation is not rare. Finally, measurement of urine osmolality is useful for the diagnosis of polydipsia and reset osmostat and could further help in the choice of therapeutic strategy because patients with low urine osmolality will benefit from water restriction or urea, whereas those with high urine osmolality (>600 mOsm/kg) would be good candidates for V_2 antagonist.

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The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was first induced experimentally in volunteers (1) and described 2 yr later in patients (2). It is one of the most frequent causes of hypoosmolality (3). Plasma sodium concentration (PNa) is the main determinant of plasma osmolality. As a result, hyponatremia usually reflects hypoosmolality. This low plasma osmolality results in a water shift from the extracellular to the intracellular fluid compartment. The overhydration of brain cells is primarily responsible for the neurologic symptoms that may be associated with hyponatremia. From the relationship PNa ≅ Nae + Ke/total body water (4), where Nae and Ke refer to the "exchangeable" quantities of these ions, it can be seen that hyponatremia can be caused by solute depletion and/or water retention.

Inhibition of both thirst sensation and ADH secretion constitutes the physiologic response against hypoosmolality. ADH secretion stops when plasma osmolality falls below 275 mOsm/kg, a setting in which PNa is usually <135 mEq/L. In the absence of ADH, the urinary osmolality (Uosm) can fall to 50 to 100 mOsm/kg. The capacity for water excretion is thus high, and hyponatremia essentially occurs only when there is a defect in renal water excretion. An exception to this rule is patients with polydipsia (frequent in schizophrenia), who drink such large volumes of fluid that they overwhelm even the normal excretory capacity, or in other potomanic patients drinking hypotonic fluids in combination with a low solute intake (beer potomania; tea and toast diet) (5,6). Several factors can potentially hinder the quantitative emission of diluted urine: Low GFR, increased proximal tubule reabsorption reducing fluid delivery to the diluting segment, or drugs (diuretics) interfering with the reabsorption of Na and chloride (Cl) in the ascending limb of the Henle's loop or in the distal tubule. The remaining major factor is ADH affecting the water permeability of the collecting ducts. Almost all hyponatremic patients have an excess of ADH, as a result of either the SIADH or effective circulating volume depletion (3). Hyponatremia is the most common fluid and electrolyte abnormality. It is associated with a much higher mortality rate than found in nonhyponatremic patients, although this is usually attributed to the underlying disease (3). When the physician is faced with a hyponatremic patient, he or she first has to confirm that hyponatremia is associated with hypoosmolality. Then he or she must answer a series of questions: What is its origin? Is it acute or chronic? Is it symptomatic? Which treatment is the most appropriate?

Because hyponatremia with hypoosmolality is caused by the retention of solute-free water, the differential diagnosis consists primarily of conditions that limit water excretion. Both effective circulating volume depletion and nonhypovolemic states of antidiuresis, usually as a result of excess of ADH, are disorders in which renal water excretion is impaired. Indeed, assessing effective arterial blood volume or effective volemia (EV) has an important place in evaluating the cause and determining the

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adequate treatment of hyponatremic patients. Different clinical and biochemical parameters have been proposed to evaluate hyponatremic patients (Table 1) (7).

This review briefly evaluates the clinical signs and detailed biochemical volume-related parameters for predicting the cause of hyponatremia and determining saline responsiveness in hyponatremic patients. Physical examination usually allows the recognition of hyponatremic causes such as heart failure, nephrosis, and hepatic cirrhosis. The presence of edema is herein an important diagnostic clue. Conversely, clinical signs of dehydration must lead to the suspicion of a depletional cause of the hyponatremia; however, physical examination is unsatisfactory to differentiate a volume-depleted hyponatremic state from a dilutional hyponatremic condition in a lot of patients (8,9). Particularly, these errors in clinical effective arterial blood volume assessment are observed in patients finally responding to isotonic saline (9,10). A majority of them are at first judged to be in a normovolemic state on clinical grounds, and the usefulness of saline treatment in the patients could be questioned (9,10). Although the history and physical examination often provide important clues to the cause of hyponatremia, identification of a subtle degree of volume depletion or edema may

Table 1. Clinical and biological data generally allowing differentiation between appropriate and inappropriate ADH secretion in patients with hypoosmolality[a]

Parameter	Appropriate Diuresis		Inappropriate Diuresis
	Hypervolemic (↑ ↑ECV; ↓EABV)	Hypovolemic (↓ECV; ↓EABV)	Euvolemic (↑ECV; ↑EABV)
History	Chronic heart failure, cirrhosis, nephrosis	Extrarenal losses (*e.g.*, gastrointestinal, sweating, burns, third space) Renal losses (*e.g.*, Addison, diuretics, bicarbonaturia, salt-losing nephropathy, cerebral salt wasting syndrome)	Drugs (*e.g.*, carbamazepine, SSRI) Neurologic diseases (*e.g.*, encephalitis, strokes) Pulmonary diseases (*e.g.*, tuberculosis, pneumonia) Cancer (*e.g.*, oat cell carcinoma) Endocrine (*e.g.*, hypothyroidism, pituitary hypocorticism)
BP	Low	Low	Normal
Edema	+	−	−
Plasma			
ADH	↑	↑	↑ (↓[b])
Na	↓	↓	↓
urea	NL-↑	NL-↑	NL-↓
uric acid	NL-↑	NL-↑	NL-↓ (mostly <4 mg/dl)
anion gap	NL-↑	NL-↑	NL-↓
Urine			
osmolality	↑	↑	↑
Na (mEq/L)	<30	<30[c]	>30[d]
Clearance ratios (%)			
FENa	<0.5	<0.5[c]	>0.5[d]
FEurea	↓-NL (<50)	↓-NL (<50)	NL-↑
FEuric acid	↓-NL (<12%)	↓-NL (<12)[e]	>12
Test infusion		Plasma Na increases usually	Plasma Na decreases only if Uosm >530 mOsm/kg/H_2O
2 L NaCl 0.9%/24 h		Salt retention (ΔFENa t24 h-t0 <0.5%), water diuresis	Rapid salt excretion (ΔFENa t24 h-t0 >0.5%)

[a]ADH, antidiuretic hormone; ECV, extracellular volume; EABV, effective arterial blood volume; FENa, fractional excretion of sodium; FEurea, fractional excretion of urea; FEuric acid; fractional excretion of uric acid; NL, normal; SSRI, selective serotonin reuptake inhibitor

[b]ADH is low in nephrogenic syndrome of inappropriate antidiuresis (nephrogenic syndrome of inappropriate antidiuresis or syndrome of inappropriate secretion of antidiuretic hormone type D).

[c]Unless salt depletion is of renal origin.

[d]If salt intake is normal.

[e]Urate clearance can be increased in hyponatremia related to cerebral salt-wasting syndrome (46) or liver cirrhosis (47).

be difficult. As a result, laboratory testing is almost always required to establish the diagnosis. We discuss first the utility of measuring serum and urine osmolality and then the biologic markers of SIADH.

Serum Osmolality and Nonhypotonic Hyponatremia

When the origin of hyponatremia is not obvious, measurement of the osmolality is prudent to be sure that we are not in the presence of a nonhypotonic hyponatremia. When the measured osmolality is normal, is increased, or exceeds the calculated one [2 × Na mmol/L + glucose mmol/L (or mg/dl ÷ 18) + Urea mmol/L (or mg/dl ÷ 6)] by >10 mOsm/kg, it suggests the presence of an osmolal gap. This occurs either when there is a decrease in the water content of the serum or when there is addition of a solute other than urea or glucose in the serum. Approximately 93% of the normal serum is represented by water. Na is diluted only in the aqueous phase, when its mean concentration is 154 mEq/L (154 × 0.93 = 142 mEq/L). Thus, a major increase in triglyceride or protein will artifactually decrease the SNa concentration; however, these macromolecules do not influence the serum osmolality. It has been estimated that for each mg/dl of lipid, the SNa concentration will artifactually decrease by 0.002 mEq/L and that a decrease of 0.25 mEq/L will be observed for each gram of protein above 8 g/dl (11). With the use of direct Na ion-specific electrodes instead of flame photometry, lipids or proteins have lower influence on SNa measurement, but, unfortunately, many instruments dilute the sample before measurement so that there could be an error on water volume of the serum. Administration of large volume of γ globulins (2 g/kg over 2 to 5 d) is a widely known factor for "pseudohyponatremia" (12) (mean decrease in SNa (SNa) of approximately 3 mmol/L).

The addition of sugar additives (*e.g.*, glucose, sucrose, maltose) to intravenous immunoglobulin formulations to prevent Ig aggregation has reduced the frequency and severity of systemic reactions but has increased the frequency of renal adverse effects, including acute renal failure (13). Translocational hyponatremia and hyperkalemia after intravenous immunoglobulin therapy, although not clinically relevant in patients with normal renal function, may be of clinical significance in patients with severely compromised renal function, resulting in impaired sugar additives excretion (14,15); most cases have been reported with sucrose (14).

When hyperproteinemia is caused by accumulation of cationic γ globulins (*e.g.*, IgG myeloma), another mechanism contributes to the reduction of the SNa value, the cations of γ globulin partly substituting for Na in balancing serum Cl. This reduction results in an increase in serum Cl concomitantly with a decrease in SNa concentration (11,16). This hyponatremia is limited to the plasmatic compartment, where paraproteins are present in appreciable quantities. The only appropriate treatment is that of the underlying protein or lipid disorders.

Generally, tonicity is more important for the organism than is osmolality. Tonicity is the concentration of solutes that have the capacity to exert an osmotic force across membrane and thereby initiate a movement of water into or out of cells depending on the gradient. Thus, because urea and some other low molecular weight substances such as ethanol, methanol, and ethylene glycol rapidly penetrate cells, they exert no effective osmotic force across most body membranes. Hence, hyponatremia associated, for example, with severe azotemia represents a true hypotonic state in regard to the cells and this despite a normal or high osmolality (depending on the level of uremia). Water movement across semipermeable membranes rapidly dissipates any pathologic attempt to create a transcellular concentration gradient, so the determination of the extracellular osmolality allows determination of the intracellular osmolality.

"Translocational hyponatremia" is observed when the patient has accumulation in the extracellular fluid (ECF) of a solute that does not penetrate the cell (glucose, mannitol, sucrose, sorbitol, glycerol, maltose, glycine, radiocontrast agents) and that draws water from the intracellular compartment. Recently, it was shown that a 100-mg/dl increase in glucose concentration induced a 2.4-mEq/L decrease in Na concentration (17), although there is probably no valid formula because of many other factors (*e.g.*, volume increase, degree of ECF volume expansion or contraction). If hyponatremia is associated with hypoosmolality, then the physician must look at some serum and urine parameter to establish its origin and its treatment. We discuss the biologic markers of SIADH.

Urine Osmolality

Urine osmolality can be measured on a spot collection concomitant with SNa measurements. To diagnose SIADH, the following criteria are needed (18) (see Table 1):

1. hypoosmolality
2. inappropriately concentrated urine (>100 mOsm/kg H_2O, although usually higher than serum)
3. natriuresis >30 mEq/L (depending on Na intake)
4. reversal of renal Na wasting and correction of hyponatremia after water restriction
5. normal renal, adrenal, thyroid, cardiac, and liver function and no signs of volume depletion (*e.g.*, absence of diuretic intake)

In fact, urine osmolality measurement is useful to detect polydipsia-related hyponatremia (Uosm <100 mOsm/kg), a diagnosis that is usually suspected by the medical history (*e.g.*, schizophrenia, beer potomania) and to detect "reset osmostat"-related hyponatremia (see later). Otherwise, measurement of urine osmolality alone is not sufficient to diagnose SIADH, because urine osmolality is also elevated in hypervolemic or hypovolemic hyponatremia (see Table 1). The high urine osmolality in these conditions is mainly due to high urea concentration, which allows electrolyte-free water excretion (19), and urine Na (UNa) concentration is <20 to 30 mEq/L.

Because regulatory mechanisms of Na excretion are intact in SIADH, extreme dietary Na restriction can lead to a nearly Na-free urine, whereas a large Na load is typically followed by a rapid increase in Na excretion (20) (see later).

In SIADH, hyponatremia initially results mainly from water retention, but urinary solute loss also plays an important role. Excess natriuresis follows water retention and mainly exceeds

the intake when volume expansion is relatively acute. After a few days, the Na balance is reestablished and a decline in the hydroosmotic effect of ADH is observed (vasopressin escape) (1,21).

It has been shown that the renal escape to vasopressin effect is due to a decrease in kidney aquaporin 2 levels (22) and V_2 receptors (23). Inhibition of nitric oxide and prostaglandin synthesis was able to increase aquaporin 2 level and therefore avoid the vasopressin escape phenomenon (24). Several experimental studies have indicated that angiotensin II (AngII) can increase V_2R expression, so the low AngII concentration observed in SIADH could contribute to the escape (25). In SIADH UNa is usually >30 mmol/L (or fractional excretion of Na [FENa] >0.5%; see Utility of UNa Concentration (and Fractional Na and Urea Excretion) Measurements), and there is no edema because fluid retention rarely exceeds 4 L, part of which is localized intracellularly.

When studying the relationship between ADH and plasma osmolality variation obtained by saline hypertonic infusion in patients with SIADH, four subtypes of the syndrome have been described (26). Type A is associated with high, erratic fluctuations of ADH unrelated to PNa concentration (30% of the cases), type B is represented by a slow constant "leak" of ADH that is also unrelated to SNa increase (30% of the cases), and type C corresponds to "reset osmostat" (also 30% of the cases). In this last group, plasma arginine vasopressin (AVP) and urine osmolality are usually low or maximally suppressed in the basal hyponatremic state; however, during infusion of hypertonic saline, they begin to increase "inappropriately" in close correlation with plasma osmolality and Na long before the hyponatremia is corrected. This pattern seems to be due to downward resetting of the entire osmoregulatory system (26).

Measurement of urine osmolality in SIADH could also help in deciding which treatment to use. If urine osmolality is very high (>600 mOsm/kg H_2O), then water restriction should be severe to maintain normonatremia (<1000 ml/d). These patients will benefit most from V_2 antagonists (27–29). Patients with relatively low and fixed urine osmolality (300 to 400 mOsm/kg H_2O; type B SIADH) could easily be treated by water restriction or by being given an osmotic load such as urea (15 to 30 g/d) (29,30), which will induce a large diuresis. Malignancy, numerous drugs, and pulmonary and neurologic diseases are known to be associated with SIADH.

In the last 10% of patients with SIADH, there is no identifiable abnormality in the osmoregulation of AVP secretion (type D). Water retention in two children was shown secondary to an activating mutation of the V_2R (31). This nephrogenic syndrome of inappropriate antidiuresis is an X-linked condition that affects mainly men but could also affect women. This mechanism of hyponatremia must be suspected in patients who are resistant to V_2 antagonist and have low AVP concentration despite high urine osmolality (32).

Utility of UNa Concentration (and Fractional Na and Urea Excretion) Measurements

As previously mentioned, it is sometimes difficult to differentiate the hypovolemic (who must be treated by solute repletion) from the euvolemic patient (in whom therapy must eliminate the excess of water) on clinical grounds. Usually, when the solute loss is extrarenal (gastrointestinal, excessive sweating), it is hypotonic and should lead to hypernatremia; however, patients often compensate for this loss with hypotonic solution or pure water, thus eventually leading to hyponatremia.

Depending on the degree of water retention, we can understand that clinical detection of ECF volume depletion could be difficult and that prerenal azotemia may be lacking. In two studies (8,9), approximately 50% of the patients who had salt depletion were not detected clinically or by history.

The best treatment if loss of extracellular electrolytes is responsible for the hyponatremia is isotonic saline infusion (2 to 3 L/d, or more if severe), which, by correcting the Na pool and expanding the circulating volume, will decrease the secondary ADH secretion and allow kidneys to eliminate electrolyte-free water. Laboratory tests can help us to distinguish hypovolemic from euvolemic hyponatremic patient (SIADH; see Table 1). The most useful and inexpensive one is the determination of Na concentration in a spot urine sample, which is <30 mEq/L in most saline-responsive hyponatremic patients and >30 mEq/L in saline nonresponders (SIADH); however, even in a patient with hypovolemia, it is not unusual for UNa to reach values as high as 50 to 60 mEq/L (9,10,33), particularly in older people, who may have slower adaptive mechanisms for retention of Na when EV is decreasing. The determination of the FENa in these patients shows values <0.5% (9,33), offering a more reliable test than a simple UNa concentration. Tubular handling of the electrolytes, urea, and uric acid are highly influenced by the "effective vascular volume." Tubular reabsorption of a substance can be evaluated by measurement of the FE of that filtered substance. This is easily obtained by measuring the concentration of creatinine, by measurement of the substance in a spot urine collection, and by the same measurement made concomitantly in the serum [FE.X (in %) = Ux/Px P/Ucreat × 100]. In patients with salt depletion, urea and uric acid clearance decrease proportionally more than creatinine clearance, so the respective FE is reduced (see later for the utility of their measurement). Low UNa is rarely observed in SIADH and when present reflects low solute intake (anorexia) or salt-depleted (SD) SIADH (10).

In a recent series of SD hyponatremic patients, we observed that 30% (mostly patients with low diuresis) have UNa >30 mEq/L (Figure 1) (33). FENa <0.5% allows us to recognize of all our SD patients. Unfortunately, 42% of our patients with SIADH had these same low FENa levels (10). FE of urea (FEurea) <50% was observed in 80% of our SD patients but also in 48% of the patients with SIADH. We discouraged the use of one biochemical parameter on its own in the prediction of saline responsiveness. We proposed the combined use of FENa and FEurea (9). FENa >0.5% or FEurea >55% was proposed as the most useful predictor of saline unresponsiveness; however, low diuresis decreases both FENa (34) and FEurea (35). For patients with low diuresis, recognized on a simple urinary spot by urinary/plasma creatinine ratio (U/P creat) >140, the discriminative limits of FENa and FEurea should be adapted. For such

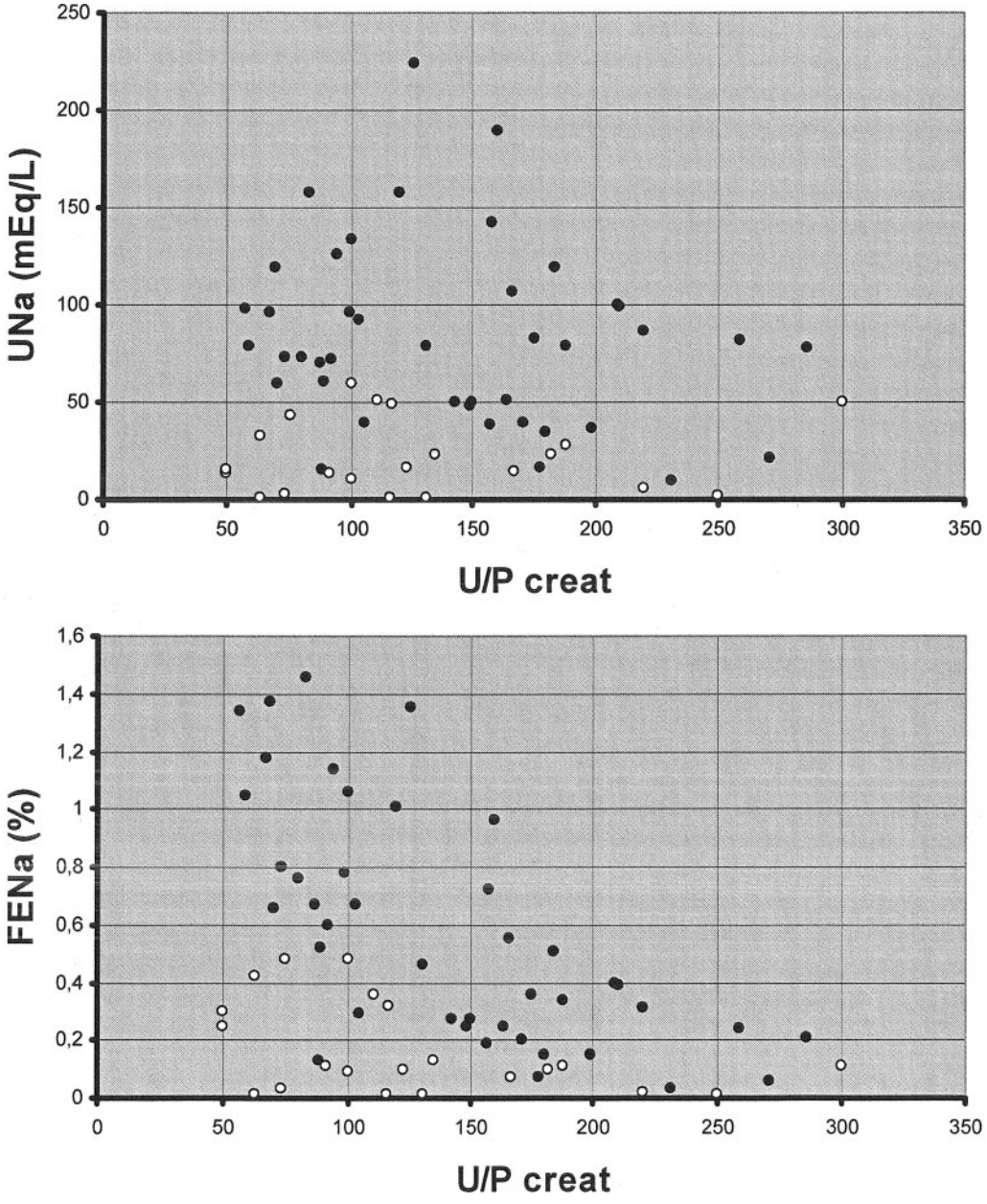

Figure 1. (Top) A urine sodium concentration (UNa) of approximately 30 mEq/L is observed frequently in patients with hyponatremia secondary to syndrome of inappropriate secretion of antidiuretic hormone (SIADH; ●) or to salt depletion (SD; ○). (B) All of the patients with SD presented a fractional excretion of Na (FENa) <0.5%, but low values are also observed in SIADH when the urinary flow is low (urinary/plasma creatinine ratio [U/P creat] >140). Data from reference (33), with permission from S. Karger AG.

patients, the combined use of FENa and FEurea remains useful, as long as we use 0.15% for the limit of FENa and 45% for the limit of FEurea (33) (Figure 2). Hyponatremic patients with low diuresis (U/P creat >140), presenting either a FENa value >0.15% or a FEurea value >45%, do not respond to isotonic saline and can be considered patients with SIADH (33).

In some patients, a test infusion of isotonic saline is helpful to determine the precise cause of the hyponatremia. This procedure is especially useful in the differential diagnosis between SD patients and patients with SIADH, when FENa and FEurea values are close to the proposed differential values (although with caution to avoid a to rapid increase in SNa). It is also useful to unmask SD patients with SIADH, presenting an initial biochemical profile undistinguishable from SD patients (10). Such SD patients with SIADH can in fact only be recognized after saline administration. In SD, PNa usually increases with only a mild increase in FENa (<0.5% after 2 L of isotonic saline over 24 h) (9,10); however, in SIADH, salt excretion rapidly occurs after saline infusion without high modification in PNa. A rapid increase in FENa (>0.5% after 2 L of isotonic saline over 24 h), without correction of PNa, correlates with inappropriate ADH secretion. A reliable classification of the cause of

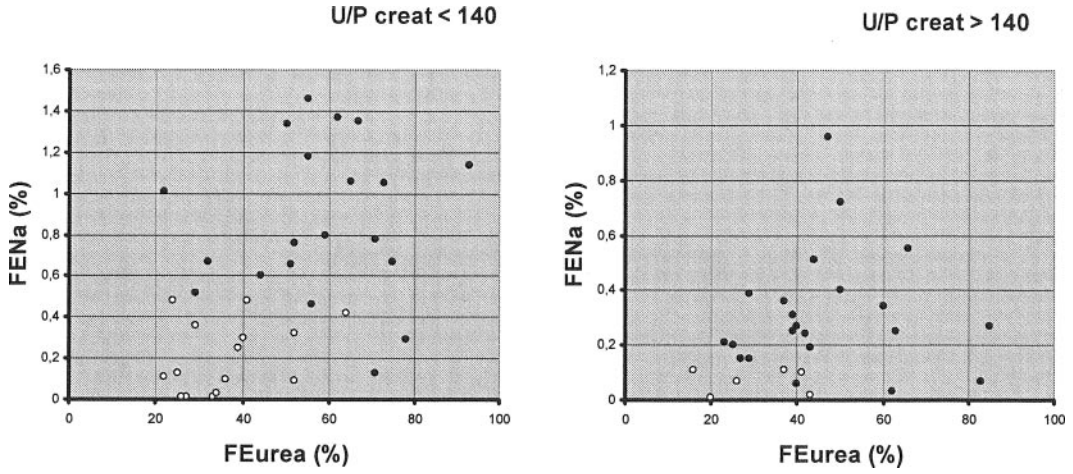

Figure 2. Relationships between fractional excretion of Na (FENa) and FE of urea (FEurea) in 20 patients with SIADH (●) and 15 SD patients (○) with U/P creat <140 (left) and 22 patients with SIADH and six SD patients with U/P creat >140 (right). When U/P creat is <140, SD patients are all but one, localized in the area described by FENa <0.5% and FEurea <55%. Patients with SIADH differ from these by either a FENa >0.5% or a FEurea >55%. When U/P creat is >140, SD patients cluster still together, but the recognition area is now restricted to a lower FEurea and especially much lower FENa limit. All SD patients are found within the area determined by FEurea <45% and FENa <0.15%, and all but one patient with SIADH has either a FEurea value >45% or a FENa value >0.15%. Reprinted from reference (33), with permission from S. Karger AG.

hyponatremia by test infusion with isotonic saline cannot be based only on the evolution of PNa. Although an increase of PNa of 5 mEq/L has been proposed as indicative for depletional hyponatremia (8), we observed that 29% of our SD patients did not increase their PNa with 5 mEq/L (10) and that 30% of true patients with SIADH responded surprisingly well to isotonic saline with an increase of PNa of at least 5 mEq/L (36).

The correct interpretation of this test suggests analysis of evolution of both PNa and FENa. Patients with SIADH and a fixed urine osmolality of approximately 300 mOsm/kg (SIADH type B) will increase SNa by 5 mmol/L if infused with 2 L of isotonic saline over 24 h (Figure 3). These patients must not be confounded with SD patients.

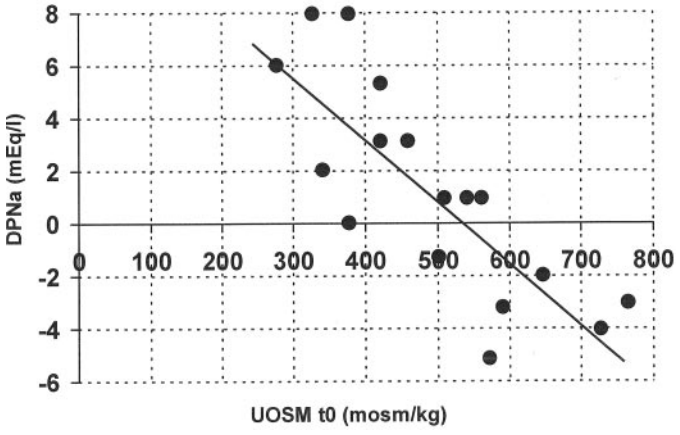

Figure 3. Significant correlation between the initial urine osmolality (Uosm T0) and the variation in plasma sodium (DPNa) after 2 L of isotonic saline in 17 patients with SIADH after water restriction ($y = -0.024x + 12.9$; $r = -0.81$; $P < 0.001$. Reprinted from reference (36), with permission.

Although such responses are generally considered as evidence for depletional hyponatremia (8), they can also be observed in SIADH patients. They can however be differentiated from patients with depletional hyponatremia by their high urinary salt excretion, since salt-depleted hyponatremic patients conserve salt as long as hyponatremia persists. SIADH patients with urine osmolality higher than 530 mOsm/kg H_2O will, as expected, decrease their SNa after isotonic infusion (36) (Figure 3).

Serum Creatinine, Urea, and Urate

Hyponatremia in young patients with SIADH is usually associated with low plasma creatinine concentration, whereas this is not the case in old patients with SIADH (37,38). SIADH is also associated with low plasma urea levels as a result of a high renal clearance (39), whereas in hyponatremia that is caused by salt depletion, plasma urea usually is increased as a result of an abnormal low FEurea (40) (prerenal uremia). Unfortunately, the usefulness of plasma urea and FEurea in discriminating SIADH and SD is limited by an important degree of "overlapping" values. We noted that plasma urea values >30 mg/dl were observed in 80% of patients with SD, whereas plasma urea values <30 mg/dl were seen in 80% of patients with SIADH. Eighty percent of the patients with SD hyponatremia presented FEurea values <50%, but only 50% of the patients with SIADH showed FEurea value >50% (10). One of the explanations for such overlapping results in plasma urea and FEurea is age, to which no attention is usually paid. It is widely known that glomerular filtration decreases with age, but this is not associated with an increase in plasma creatinine, as a result of a concomitant age-related decrease in muscle mass and creatinine production. Moreover, there is an age-related

increase in plasma urea level and decrease in fractional urea excretion (Figure 4), which explains the difference in urea and FEurea between young and old patients with SIADH (mean urea and FEurea in young patients with SIADH 18 mg/dl and 58%, respectively, and in old patients 29 mg/dl and 44%, respectively) (38).

As for urea, the level of serum uric acid is known to be partially dependent on its renal clearance, which is influenced by different factors, one of the most important being EV. By controlling renal water excretion, ADH is generally considered to influence the EV. It seems likely that regulation of renal Na excretion and retention to maintain extracellular volume influences renal uric acid and urea clearance in a similar way. Dorhout Mees *et al.* (41) were the first to report that hyponatremia induced in volunteers by the administration of AVP and water was associated with a larger decrease in serum uric acid (approximately 50%) than expected for the degree of dilution (approximately a 10% decrease in SNa concentration). The decrease in serum uric acid concentration mainly resulted from high uric acid clearance (proportionally higher than the increase in glomerular filtration). These investigators showed in two patients with SIADH that normalizing natremia by water restriction normalized the fractional uric acid excretion and serum uric acid level, despite persistence of the initial disease. This finding suggests that expansion of the extracellular volume was responsible for the increase in fractional uric acid excretion. The increase in uric acid fractional excretion in the SIADH is due to a decrease in tubular reabsorption (42), mainly localized at presecretory and postsecretory sites of the tubule, whereas urate secretion seems to be appropriate for the level of uricemia (43).

Beck (44) reported that hyponatremia secondary to SIADH is generally associated with a serum uric acid level <4 mg/dl; however, values are >5 mg/dl in patients with hyponatremia associated with a decrease in the EV. Since this initial observation, hyponatremia associated with hypouricemia (<4 mg/dl) and a high fractional uric acid excretion (>12%; >16% in the elderly) has been reported in other conditions, such as hypocorticism, diuretics, potomania (45), and renal salt wasting (46). In cirrhosis, this finding could be due to low a synthesis and/or high clearances (47).

As previously mentioned in cases of SIADH, urea levels also may be disproportionately low for the degree of dilution. This results from a high urea clearance, mainly secondary to a decrease in tubular urea reabsorption as a result of increased volemia (39).

Hypouricemia (<4 mg/dl) is more frequently observed than hypouremia in cases of SIADH, because high salt excretion is associated with a normal urea clearance. Uric acid clearance, however, is not influenced by salt excretion (at least in the normal range for salt excretion) (48).

The high volemia observed in SIADH is associated with a decrease in proximal Na reabsorption and indirectly affects urate reabsorption, which is located mainly in the proximal tubule (49). The result is an increased Na delivery distal to the proximal tubule, where further reabsorption occurs, and finally achieving Na excretion within the normal range. Urate reabsorption, however, does not occur in a significant manner distal to the proximal tubule, and urate clearance remains high. We recently observed in volunteers that hyponatremia induced by the administration of dDAVP (a potent V_2 agonist) increases urate clearance to a much lower extent (±30%) than in patients

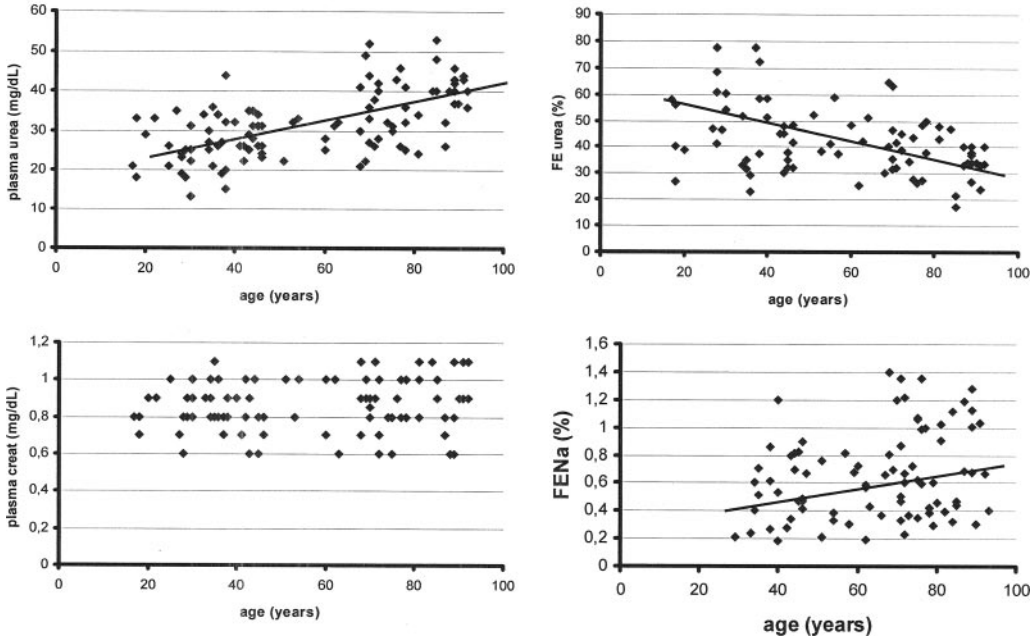

Figure 4. (Left) Relationship between plasma urea and age (top; y = 0.229 x + 18.26; $r = 0.62$; $P < 0.001$) and lack of correlation between plasma creatinine and age in 107 normal individuals. (Right) Relationship between FEurea and age (top; y = 0.226x + 55; $r = -0.41$; $P < 0.001$) and between FENa and age (bottom; y = 0.0046x + 0.365; $r = 0.27$; $P < 0.02$) in 87 normal individuals with an U/P creat between 50 and 150. Adapted from reference (38), with permission.

with SIADH (±100%) (50). This difference is reported despite a similar degree of hyponatremia, natriuria, and volume expansion (indirectly estimated by the level of hypoproteinemia) (51).

These data suggest that the higher urate clearance observed during hyponatremia related to SIADH is the consequence of an increased EV and that V_1 receptor stimulation also contributes to it. The high FE of uric acid typically observed in hyponatremia related to SIADH is also influenced by the chronicity of hyponatremia (>12 h) and the glomerular filtration (52).

Hematocrit, Protein, Albumin, and Red Blood Cell Mean Corpuscular Volume

Hyponatremia related to inappropriate antidiuresis is associated with an increase in total body water (body weight rarely increased by >4 kg) and a decrease in hematocrit and protein concentration the first days of its induction (51). The expansion of the vascular compartment in this model depends essentially on the plasmatic volume. The mean corpuscular volume increases only slightly, because of rapid adaptation of the red cells to the hypoosmolar environment (by intracellular solute lost) (51). When hyponatremia is of longer duration (>1 wk), it has been shown in the animal model that extracellular volume could normalize nearly completely (53), and indirect data in humans have also shown a near normal protein concentration in patients with chronic SIADH, reflecting likely a complete adaptation to hypotonicity (by solute loss) (52). So hematocrit and protein concentration are usually not highly helpful in the diagnosis of SIADH (inasmuch as many other factors such as simply dilution interferes with their value). A high hematocrit would suggest that the basis for hyponatremia is a deficit of Na^+. It is interesting to note that atrial natriuretic peptide is increased as expected during acute water retention (53) but that it normalized after a few days of hyponatremia (52,54,55).

Anion Gap and Bicarbonate in SIADH

In hyponatremia related to SIADH, it is expected that the anion gap (AG) decreases proportionally to the magnitude of the dilution (56–58), but when measured, it decreased more than expected (45). Plasma bicarbonate concentration remains usually normal despite dilution in the SIADH (2,59,60), but because the decrease in serum Cl concentration is of the same magnitude than for SNa, this suggests that the AG will decrease more than one would expect from the simple dilutional effect (45).

The numerous organic acids (OA) present in the serum (at least 29) (61) were not measured in SIADH; it is possible that the renal clearance of many OA is enhanced in response to the expanded volemia as is the case for uric acid. Another possibility is that dilution induces a diffusion of bicarbonate outside the cell (62) and that this is associated with an intracellular shift of OA. Another mechanism could be a modification of the anionic charges of albumin, which has been reported to be influenced by volemia: Decrease in the negative charge of albumin during volume expansion and increase during hypovolemia (63). In hyponatremia associated with hypovolemia, the AG stays normal or is increased (45,63).

Endocrine disorders, particularly hypopituitarism, must be excluded in patients who present with hyponatremia related to inappropriate antidiuresis. Low bicarbonate level is a frequent observation in hyponatremia related to ACTH deficiency (mean value of total CO_2 20.5 ± 3 mmol/L) and could help to differentiate it from classical SIADH (mean value 25.5 ± 2.4 mmol/L) (64,65).

In chronic nonendocrine SIADH, the relative hyperaldosteronism observed is due to the low Na concentration, which stimulates directly aldosterone secretion by the adrenal gland (66). Cortisone plays a critical role in the development of this hypotonic-related hyperaldosteronism (64,65). In patients who present with hyponatremia related to ACTH deficiency, low aldosterone concentrations are observed and explain why a metabolic alkalosis does not develop, and a compensated respiratory alkalosis is usually observed (64,65).

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Disclosures

None.

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