Value of Fractional Uric Acid Excretion in Differential Diagnosis of Hyponatremic Patients on Diuretics

Wiebke Fenske,* Stefan Störk,* Ann-Cathrin Koschker, Anne Blechschmidt, Daniela Lorenz, Sebastian Wortmann, and Bruno Allolio

Endocrinology & Diabetes Unit (W.F., A.-C.K., A.B., D.L., S.W., B.A.) and Cardiology Unit (S.S.), Department of Medicine I, University of Wuerzburg, 97080 Wuerzburg, Germany

Background: The syndrome of inappropriate antidiuresis (SIAD) is the most frequent cause of hyponatremia. Its diagnosis requires decreased serum osmolality, inappropriately diluted urine (*e.g.* >100 mOsm/kg), clinical euvolemia, and a urinary sodium (Na) excretion (U-Na) more than 30 mmol/liter. However, in hyponatremic patients taking diuretics, this definition is unreliable due to the natriuretic effect of diuretics. Here, we examined the diagnostic potential of alternative laboratory measurements to diagnose SIAD, regardless of the use of diuretics.

Methods: A total of 86 consecutive hyponatremic patients (serum Na <130 mmol/liter) was classified based on their history, clinical evaluation, osmolality, and saline response to isotonic saline into a SIAD and a non-SIAD group. U-Na, serum urate concentration, and fractional excretion (FE) of Na, urea, and uric acid (UA) were measured in all subjects. The accuracy to diagnose SIAD was assessed using receiver operating characteristic analysis.

Results: A total of 31 patients (36%) had a diagnosis of SIAD, and 55 (64%) were classified as non-SIAD. There were 57 patients (68%) who were on diuretics (15 in the SIAD group, 42 in the non-SIAD group). In the absence of diuretic therapy, SIAD was accurately diagnosed using U-Na (area under the receiver operating characteristic curve 0.96; 0.92–1.02). However, in patients on diuretics, the diagnosis was unreliable (area under the curve 0.85; 0.73–0.97). There, FE-UA performed best compared with all other markers tested (area under the curve 0.96; 0.92–1.12), resulting in a positive predictive value of 100% if a cutoff value of 12% was used.

Conclusion: FE-UA allows the diagnosis of SIAD with excellent specificity. Combining the information on U-Na and FE-UA leads to a very high diagnostic accuracy in hyponatremic patients with and without diuretic treatment. **(*J Clin Endocrinol Metab* 93: 2991–2997, 2008)**

Hyponatremia is the most common electrolyte disorder, occurring in up to 30% of hospitalized patients (1). The most frequent cause of hyponatremia is the syndrome of inappropriate antidiuresis (SIAD), followed by hyponatremia associated with depletion of the effective arterial blood volume (EABV). Many cases remain asymptomatic. However, a careful diagnostic workup of the cause of hyponatremia is important because the various underlying diseases may require completely different therapies (2). False therapy as a result of misdiagnosis may lead to significant clinical consequences (2–4).

In the diagnostic workup of hyponatremia, the evaluation of the status of extracellular fluid volume (ECFV) is critical because it allows best to differentiate dilutional from depletional hyponatremia, thus determining the treatment strategy (3). However, the differentiation between extracellular hypovolemia and euvolemia can be difficult (4). Determination of the sodium (Na) concentration from spot urine [urinary Na excretion (U-Na)] or fractional urine Na excretion (FE-Na) is diagnostically useful and considered the reference standard to differentiate decreased EABV in hypovolemic or hypervolemic disorders (U-Na <30

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* W.F. and S.S. contributed equally to this work.

Abbreviations: AUC, Area under the curve; AVP, arginine vasopressin; CI, confidence interval; CSWS, cerebral salt wasting syndrome; EABV, effective arterial blood volume; ECFV, extracellular fluid volume; FE, fractional excretion; Na, sodium; ROC, receiver operating characteristic; SIAD, syndrome of inappropriate antidiuresis; S-UA, serum uric acid concentration; UA, uric acid; U-Na, urinary sodium excretion.

mmol/liter) from euvolemic hyponatremia in SIAD (U-Na >30 mmol/liter) (5). However, U-Na and FE-Na are of limited diagnostic utility in subjects on diuretic therapy due to the inhibition of tubular Na reabsorption, leading to increased renal Na excretion. Accordingly, in clinical trials these patients were either excluded or categorized *a priori* as diuretic-induced hyponatremia (6, 7).

Because diuretics are among the most widely prescribed drugs, frequent use among patients with hyponatremia is to be expected. Thus, the present diagnostic workup of hyponatremia is often hampered in hyponatremic patients on diuretic treatment, and reliable alternative parameters are needed for a rapid classification of these patients.

To this end, markers like the fractional excretion (FE) of urea and uric acid (UA) and serum UA concentration (S-UA) have been proposed because no interference with diuretics is expected (7, 8). However, their diagnostic utility in patients on diuretic therapy is unknown.

Accordingly, we determined the diagnostic utility of the established reference standard (U-Na and FE-Na) in comparison with alternative volume-related parameters (FE-urea, FE-UA, and S-UA) to differentiate SIAD from EABV depleted hyponatremia, regardless of the use of diuretics.

Patients and Methods

Study design and population

Between April and November 2007, all consecutive hyponatremic patients presenting at the Medical Department of the University of Würzburg, a 300-bed secondary and tertiary care university hospital, were screened. Eligibility criteria were a serum Na concentration of less than 130 mmol/liter on admission (reference range 135–145 mmol/liter), serum osmolality less than 280 mOsm/kg H_20 [either measured or using the following formula: P_{osm} (mOsm/kg H_2O) = 1.86 × serum [Na^+] (mmol/liter) + glucose/18 (mmol/liter) + BUN/6 (mmol/liter)], and age older than 18 yr.

If the pharmacotherapy at hospital admission could not be reliably specified, patients were not eligible. In addition, patients with hyponatremia due to acute or chronic renal failure (serum concentration of creatinine >3 mg/dl) and patients with psychosis-intermittent hyponatremia-polydipsia syndrome were also ineligible. The study was approved by the Ethical Committee of the University of Würzburg (No. 33/07), and written informed consent was obtained from all patients before participation.

The underlying cause of hyponatremia was carefully determined. A detailed medical history was obtained emphasizing dietary intake and pharmacotherapy, followed by a standardized clinical and biochemical evaluation. ECFV status was assessed as described by Chung (4) and McGee (9) *et al.*, with special attention to orthostatic changes in pulse rate and blood pressure. Orthostatic hypotension and orthostatic change in pulse rate were defined as reduction in systolic blood pressure of more than or equal to 20 mm Hg and the increase in pulse rate of more than or equal to 30% after 1 min in the upright position compared with the supine position, respectively.

Patients were categorized into a SIAD group and a non-SIAD group, without information on index test results and U-Na. A diagnosis of SIAD was accepted if all of the following criteria were present: inappropriately diluted urine (>100 mOsm/kg H_2O); clinical euvolemia (*i.e.* no clinical signs of ECFV depletion or ECFV expansion); and normal renal, adrenal, and thyroid function. Patients not fulfilling any of these conditions were classified as the non-SIAD group. The non-SIAD group was composed of three subgroups: hyponatremia due to extracellular volume depletion, hyponatremia due to extracellular volume expansion, and diuretic-induced hyponatremia. Hyponatremia due to extracellular volume depletion was diagnosed in patients with historical (*e.g.* vomiting, diarrhea), clinical, and/or laboratory indications of hypovolemia (*e.g.* U-Na <30 mmol/liter or salt retention after isotonic saline infusion).

In case of diagnostic uncertainty, the discrimination between SIAD and hypovolemic hyponatremia was based on a test infusion of isotonic saline. Patients with a sustained increase in serum Na of more than or equal to 5 mmol/liter and a ΔFE-Na less than 0.5% after 2-liter saline administration in 24 h were classified as Na depleted. In the remaining patients, a diagnosis of SIAD was accepted.

Patients with an excess of ECFV have been recognized by clinical examination because of the presence of edema and suffer from diseases as congestive heart failure or liver cirrhosis.

Patients with normalizing hyponatremia after withdrawal of diuretics were considered diuretic-induced hyponatremia.

Laboratory assessment

Blood samples and urine specimens were taken between 1000 and 1300 h (2–5 h after drug administration). Biochemical evaluation included the venous sampling of serum glucose, urea, creatinine, UA, Na, potassium, chloride, total proteins, albumin, triglycerides, osmolality, cortisol, ACTH, plasma renin concentration, aldosterone, and TSH. Urine specimens were tested for osmolality, glucose, urea, creatinine, UA, Na, potassium, chloride, and proteins. Using urinary spot analysis, we estimated the Na excretion as well as the percent FE of filtered Na, urea, and UA by the formula: $FE_x = (U_x \times P_{Creatinin}/U_{Creatinin} \times P_x) \times 100$. There was no time interval between the measurement of the index test and the measurement of the reference standards (U-Na, FE-Na).

Laboratory measurements were done using established and quality controlled methods. Automated chemical analysis was performed in the Central Core Laboratory of the Medical University. Urine and serum

TABLE 1. Characteristics of patients with (n = 31) and without SIAD (n = 55)

	SIAD group (n = 31)	Non-SIAD group (n = 55)
Age (yr)	66 (15)	70 (15)
Female sex (%)	17 (55)	32 (58)
Current diuretic therapy	15 (48%)	42 (76%)
Cause of hyponatremia		
Neoplastic	15 (48%)	
Acute bacterial infection	6 (19%)	
Nausea and vomiting	4 (13%)	
AVP analogs	2 (6.5%)	
Positive pressure breathing	1 (3%)	
Idiopathic	3 (10%)	
Extracellular volume depletion		27 (49%)
Malnutrition, low-Na diet		14 (25%)
Gastrointestinal Na loss		9 (17%)
Pancreatitis		4 (7%)
Extracellular volume expansion		21 (38%)
Acute decompensated heart failure		12 (22%)
Chronic heart failure		4 (7%)
Cirrhosis and ascites		4 (7%)
Angioedema		1 (2%)
Diuretic-induced hyponatremia		7 (13%)
Hydrochlorothiazide		5 (9%)
Hydrochlorothiazide plus furosemide		2 (4%)

Data are mean (SD) or numbers.

TABLE 2. Biochemical and clinical data before treatment in four etiological categories of hyponatremic patients

		Non-SIAD group (n = 55)			
	SIAD group (n = 31)	Salt depletion (n = 27)	ECFV expansion (n = 21)	Diuretics (n = 7)	*P* value
Serum					
Na (mmol/liter)	124.9 (5)	123.9 (6)	125.1 (4)	121.6 (5)	0.380
Potassium (mmol/liter)	4.1 (0.4)	4.2 (0.9)	4.3 (0.5)	3.7 (0.5)	0.241
Creatinine (mg/dl)	0.8 (0.3)	1.3 (1)	1.2 (0.6)	1.3 (0.8)	0.003
Urea (mg/dl)	31.2 (16)	54.4 (38)	81.1 (60)	56.3 (50)	0.001
UA (mg/dl)	3.3 (1)	6.4 (2)[a]	8.2 (3)[a]	6.2 (4)[a]	<0.001
Hematocrit (%)	33.2 (5)	36.9 (4)	34.8 (5)	33.9 (4)	0.029
Osmolality (mOsm/kg)	252 (13)	256 (14)	269 (19)	255 (16)	0.040
Renin (ng/liter)	9.6 (5–23)	31.0 (15–98)	330.1 (54–731)	14.8 (5–257)	<0.001
Aldosterone (ng/liter)	72 (24–145)	94 (48–291)	210 (78–492)	65 (32–204)	0.007
Urinary					
Na excretion (mmol/liter)	96 (50)	29 (13)[a]	44 (21)[a]	64 (32)[a]	<0.001
Potassium excretion (mmol/liter)	42 (26)	45 (22)	45 (17)	27 (15)	0.072
Osmolality (mOsm/kg)	478 (170)	463 (218)	383 (127)	283 (103)	0.004
Clearance ratio					
FE-Na (%)	0.9 (0.5–1.8)	0.3 (0.1–0.6)[a]	0.5 (0.2–1.1)[a]	1.6 (0.4–4)	<0.001
FE-urea (%)	50 (18)	31 (15)[a]	32 (18)[a]	39 (12)	<0.001
FE-UA (%)	17 (11–23)	6 (4–9)[a]	6 (2–8)[a]	7 (4–10)	<0.001
FE-potassium (%)	12 (7–19)	14 (5–21)	17 (9–27)	16 (8–65)	0.351
Vital signs					
BP in supine position (mm Hg)	124/74 (21/12)	115/69 (19/9)	111/64 (21/11)	129/71 (18/8)	0.042
Heart rate in supine position (Bpm)	74.4 (13)	78.8 (15)	71.5 (12)	75.7 (15)	0.452
Orthostatic decrease in systolic BP (%)	3.0 (0–9)	22.0 (16–25)[a]	20.5 (13–27)[a]	6.0 (4–10)	<0.001
Orthostatic increase in heart rate (%)	10.0 (6–14)	25.0 (20–34)[a]	34.5 (25–45)[a]	6.0 (0–14)	<0.001

Data are mean (SD) or median (25th-75th percentile), respectively. BP, Blood pressure; Bpm, beats per minute.

[a] $P < 0.05$ compared with the SIAD group.

samples were analyzed using ion-selective electrodes for Na, potassium, and chloride. Osmolality was measured directly via determination of freezing point depression. Cortisol, ACTH, and TSH were measured by immunoassay (IMMULITE 2000; Siemens Medical Solution Diagnostic GmbH, Bad Nauheim, Germany). Plasma aldosterone and renin measurements were performed by RIA using commercially available assays: aldosterone (Diagnostic Products Corp., Los Angeles, CA); and renin concentration (Cis-Bio Intl., Marcoule, France).

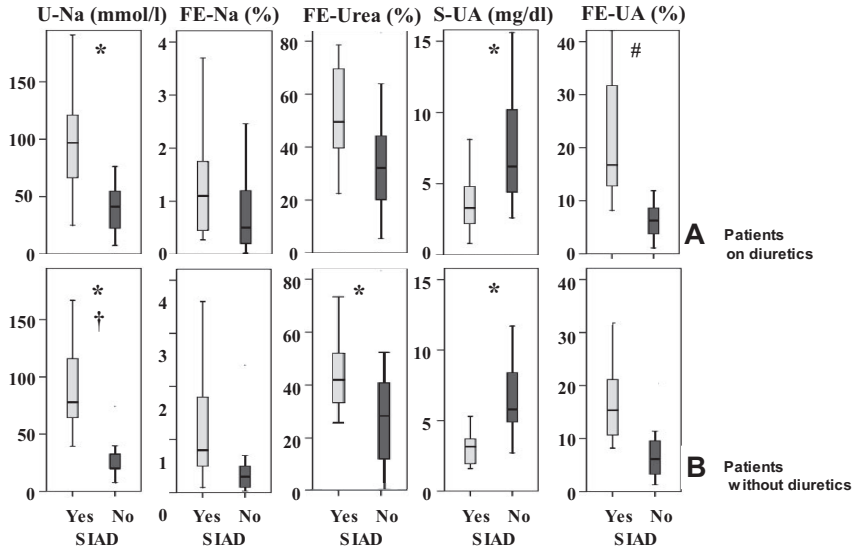

FIG. 1. Levels of U-Na, FE-Na, FE-urea, S-UA, and FE-UA in patients with SIAD (*light boxes*) and without SIAD (*dark boxes*), and with (A) and without (B) diuretic therapy. *Boxes* show median and interquartile range, and *whiskers* indicate 5th to 95th percentile. *, Bonferroni-adjusted *P* value < 0.005 for comparison between SIAD and non-SIAD groups. #, Bonferroni-adjusted *P* value = 0.002 for comparison between SIAD and non SIAD groups. †, Bonferroni-adjusted *P* value < 0.005 for comparison between patients with and without diuretic treatment.

Data analysis

Characteristics of study participants are presented as means with their SD values for normally distributed variables, medians with 25th to 75th percentile for nonnormally distributed variables, and frequencies for categorical variables. Mean values were compared by the Kruskal-Wallis test among different groups. Group comparisons between patients with and without SIAD were made using the Student's *t* test after testing for equality of variances by Levene's test. Categorical variables were compared by the Fisher's exact test and χ^2 test. To describe the diagnostic utility of the different biomarkers, standard diagnostic performance measures were calculated with their 95% confidence intervals (CIs), and receiver operating characteristics (ROCs) were plotted. The area under the curve (AUC) was calculated by the nonparametric trapezoidal rule, with its SE and 95% CI (10). Differences in the diagnostic utility between biomarkers were estimated by differences in the ROC area, considering the correlation between models because they were based on the same cases (10, 11). To account for multiple comparisons of the 10 diagnostic variables, a simple Bonferroni adjustment was made, and statistical significance was accepted at $\alpha = 0.005$ (*i.e.* 0.05/10). For the comparisons between ROC curves, the conventional *P* value of 0.05 was accepted. Statistical

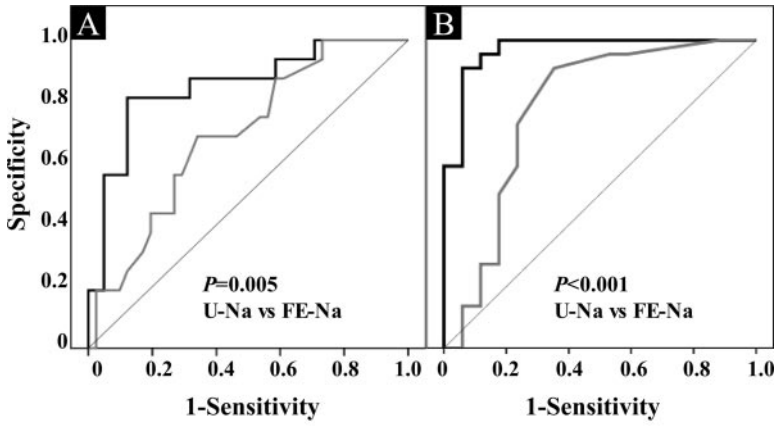

FIG. 2. Comparison of the diagnostic utility (ROC analysis) of U-Na and FE-Na to differentiate between SIAD and EABV depleted hyponatremia in patients with (A) and without (B) diuretic therapy. The *diagonal line* indicates the area of 0.5, corresponding to no informative discrimination. *P* values are for the differences between areas (see *Patients and Methods*).

analyses were performed using SPSS software (version 14.0.1; SPSS, Inc., Chicago, IL).

Results

The patient characteristics and respective causes of hyponatremia are shown in Table 1. A total of 45 patients received a test infusion of isotonic NaCl (SIAD n = 24, non-SIAD n = 21). A final diagnosis of SIAD was made in 31 patients (36%). There were 15 SIAD patients (48%) who received diuretics. Neoplastic disease, especially carcinoma of the lung, was the dominant underlying disease in patients with SIAD (48%). In three subjects no cause for SIAD could be established.

Compared with the SIAD group, subjects in the non-SIAD group (n = 55) were significantly older ($P < 0.05$), and 42 patients were on diuretics (76%). We identified 27 patients (49%) with hyponatremia due to extracellular volume depletion, 21 (38%) with hyponatremia due to extracellular volume expansion, and seven (13%) with diuretic-induced hyponatremia. In the group with hypovolemic hyponatremia malnutrition, low-Na diet and gastrointestinal Na loss were the most frequent conditions. In patients with hypervolemic disorders, the predominant diagnosis was heart failure (76%).

Results of the biochemical and clinical investigations are shown in Table 2. S-UA, plasma renin, and aldosterone values were significantly lower in the SIAD group compared with the non-SIAD group ($P < 0.001$). U-Na and FE-UA were higher in the SIAD compared with the non-SIAD group ($P < 0.01$), and FE-urea and FE-Na values were also significantly higher in the SIAD group compared with salt-depleted and ECFV expanded patients ($P < 0.05$). There was no difference in S-UA, U-Na, and in the measured clearances between patients with ECFV depletion and patients with ECFV expansion.

The values of U-Na, FE-Na, FE-urea, FE-UA, and S-UA are presented in box plots in patients with and without SIAD and in patients with and without diuretic treatment, respectively (Fig. 1). In general, there was substantial overlap of data points between the SIAD and non-SIAD groups. However, in patients on diuretic treatment, FE-UA performed best, whereas U-Na performed best in patients without diuretic treatment.

Urinary Na values less than 30 mmol/liter are commonly accepted to differentiate SIAD from EABV depleted hyponatremia (4). However, 57% of our patients in the non-SIAD group (of whom 84% used diuretics) showed U-Na values more than 30 mmol/liter and a normal urinary output (urine/serum creatinine <140). In this group, patients on diuretics had a higher median U-Na value compared with subjects not using diuretics ($P < 0.005$). For FE-Na, 81% of the patients in the SIAD group presented with values more than 0.5%, but 47% of the EABV depleted patients (of whom 82% used diuretics) also showed values more than 0.5%. FE-urea less than 55% was found in 96% of EABV depleted patients, but FE-urea more than 55% was found in only 35% of the SIAD patients.

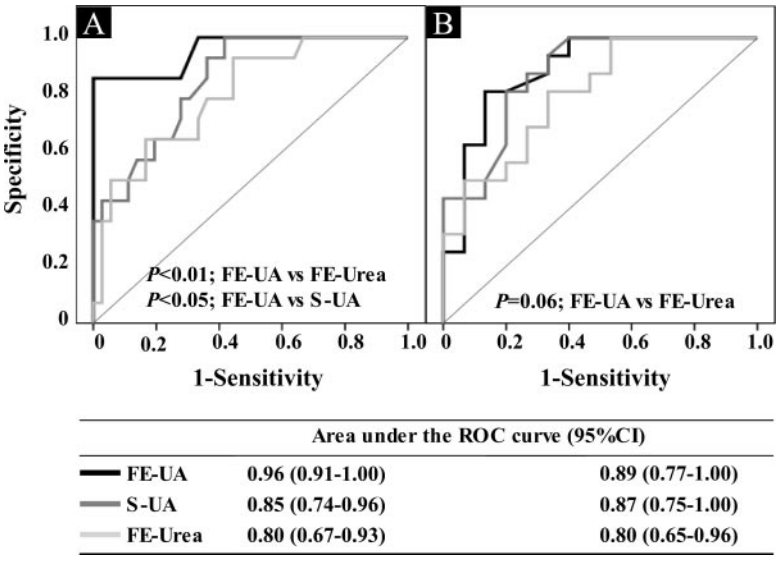

FIG. 3. Comparison of the diagnostic utility (ROC analysis) of FE-UA, S-UA, and FE-urea to differentiate between SIAD and EABV depleted hyponatremia in patients with (A) and without (B) diuretic treatment. The *diagonal line* indicates the area of 0.5, corresponding to no informative discrimination. *P* values are for the differences between areas (see *Patients and Methods*).

TABLE 3. Diagnostic test characteristics of different biomarkers (cutoff value[a]) for the diagnosis of SIAD in patients with (+) and without diuretics (−)

Test characteristic	U-Na (30 mmol/liter)		FE-UA (12%)		FE-Na (0.5%)		FE-Urea (55%)		S-UA (4 mg/dl)	
	+	−	+	−	+	−	+	−	+	−
Sensitivity	0.94	1.0	0.86	0.63	0.75	0.81	0.46	0.68	0.65	0.83
Specificity	0.24	0.69	1.0	0.87	0.47	0.71	0.96	0.94	0.76	0.83
PPV	0.39	0.83	1.0	0.83	0.37	0.78	0.87	0.94	0.55	0.87
NPV	0.89	1.0	0.95	0.68	0.81	0.81	0.82	0.68	0.82	0.79

NPV, Negative predictive value; PPV, positive predictive value.

[a] For U-Na, FE-Na, FE-urea, and S-UA, the recommended cutoff values were used (see *Patients and Methods*). For FE-UA, a cutoff value of 12% was derived from the data set.

S-UA less than 4 mg/dl was detected in 70% of SIAD patients but also in 23% of the patients diagnosed as non-SIAD (of whom 80% received diuretics). In all patients of the SIAD group, FE-UA levels were more than 8%, whereas FE-UA was less than 12% in all patients of the non-SIAD group (Fig. 1).

U-Na was useful to diagnose SIAD in patients without diuretics: the area under the ROC curve (95% CI) was 0.97 (0.91–1.00; Fig. 2A). In these patients, U-Na discriminated better compared with FE-Na ($P < 0.001$ for comparison of areas under the ROC curves), FE-urea ($P < 0.001$), and S-UA ($P < 0.05$; Figs. 2A and 3A) but performed equal to FE-UA (P = not significant). By contrast, in patients on diuretics, the diagnostic utility of U-Na was considerably lower ($P < 0.05$ *vs.* patients without diuretic treatment; Fig. 2B and Table 3). FE-urea, S-UA, and FE-UA performed similarly in both groups (Fig. 3). However, FE-UA was the only marker that showed an increased diagnostic value in patients on diuretic treatment (AUC 0.96; 0.91–1.00; $P = 0.05$).

In a sensitivity analysis, we chose five cutoff points of FE-UA to achieve a sensitivity of more than 80% and specificity of more than 70% to diagnose SIAD in patients on diuretics. A cutoff value of 12% had a sensitivity of 86%, with a specificity and positive predictive value of 100% to identify SIAD accurately (Table 3). A FE-UA cutoff value of 8% resulted in a sensitivity and negative predictive value of 100% (Table 4).

Using the combined information on U-Na and FE-UA to diagnose or exclude SIAD, these parameters allowed to classify correctly the presence or absence of SIAD in 94% of all patients.

Discussion

Our findings demonstrate that diuretics are widely used in hyponatremic patients (68% of the total study population), without necessarily being the cause of hyponatremia. In these patients, the use of U-Na or FE-Na resulted in a pronounced loss of diagnostic accuracy compared with its utility in nonusers. Although FE-Na has been considered to be superior to U-Na in diagnosing Na-depleted patients (6, 7), our data show that in patients without diuretics, U-Na is superior for diagnosing SIAD compared with FE-Na (Fig. 2).

As expected, administration of diuretics had no impact on the diagnostic utility of FE-urea, S-UA, and FE-UA. FE-UA exhibited the best overall performance to diagnose SIAD in patients on diuretics and was not inferior to U-Na in nonusers of diuretics. To put these findings into perspective, the detection of congestive heart failure using B-type natriuretic peptide resulted in an area under the ROC curve of 0.91 (12), and a diagnosis of prostate cancer using the prostate-specific antigen resulted in an AUC of 0.94 (13). A FE-UA cutoff value of 12% appeared to be optimal to confirm the diagnosis of SIAD (positive predictive value of 100%), whereas a FE-UA less than 8% excludes SIAD. Therefore, FE-UA is a simple and rapidly available tool (<1 h), which allows to diagnose SIAD with excellent specificity, closing the diagnostic gap in patients on diuretic treatment.

UA is the end product of purine metabolism in humanoid primates and is excreted predominantly through the kidneys. In contrast to Na and urea, the transport mechanisms of urate are localized exclusively in the proximal tubule. Therefore, a direct interaction with common diuretics is not to be expected. However, changes in ECFV are important factors modulating urate excretion. In healthy euvolemic subjects, FE-UA is approximately 10% (8). Contraction of ECFV decreases FE-UA, and expansion of ECFV enhances FE-UA, an effect independent of the increase in urinary flow (14). Although the mechanisms of either effects are unknown, one may speculate that urate reabsorption is indirectly coupled to Na transport by an electroneu-

TABLE 4. Sensitivity analysis of different FE-UA cutoff values to identify SIAD in patients with (+) and without diuretic treatment (−)

Cutoff value	12%		11%		10%		9%		8%	
	+	−	+	−	+	−	+	−	+	−
Sensitivity	0.86	0.63	0.86	0.75	0.86	0.81	0.86	0.75	1.00	1.00
Specificity	1.00	0.87	0.94	0.80	0.88	0.73	0.85	0.60	0.73	0.53
PPV	1.00	0.83	0.86	0.80	0.75	0.76	0.71	0.67	0.61	0.70
NPV	0.95	0.68	0.94	0.75	0.94	0.79	0.93	0.70	1.0	1.00

NPV, Negative predictive value; PPV, positive predictive value.

tral anion exchanger (15), and, therefore, an increased proximal Na reabsorption explains the decreased urate excretion in volume-depleted disorders.

Hyponatremia related to SIAD is typically associated with a high UA clearance and an abnormally elevated FE-UA that normalizes after correction of hyponatremia (15, 16). The effect of extracellular volume expansion on hypouricemia and increased FE-UA is still unclear (8). However, the fact that patients with ECFV expansion and a decreased EABV also have reduced FE-UA (Table 2) indicates that EABV is the critical determinant of FE-UA (17). Other factors may also be important. Indirect data suggest that chronicity of hyponatremia affects UA clearance in SIAD by reducing tubular UA reabsorption as a consequence of decreased intracellular anion levels during cell adaptation to hypotonicity (18). Thiazides are also considered to enhance FE-UA by increasing arginine vasopressin (AVP) activity (19, 20) or inducing up-regulation of aquaporin-2 expression (21). Other authors suspect that additional stimulation of V_1 receptors contributes to the development of high UA clearance in SIAD because hypouricemia and elevated FE-UA were not inducible by 1-disamino-β-D-AVP as compared with induction by AVP (22).

A reason why the discriminative value of FE-UA did not attract attention previously in the diagnosis of hyponatremia may be related to the fact that in most studies, patients on diuretics were either excluded or categorized *a priori* as diuretic-induced hyponatremia (7, 16).

A few clinical aspects may limit the diagnostic value of FE-UA. First, an elevated FE-UA more than 12% has also been reported in some cirrhotic patients (23) and in patients with cerebral salt wasting syndrome (CSWS) (17, 24, 25). CSWS is a rare clinical entity, including mostly patients with intracranial disorders, who present with decreased blood volume resulting from renal salt wasting (24–26). In contrast to SIAD, in which hypouricemia and increased FE-UA normalize after correction of hyponatremia (26, 27), urate transport abnormality may persist in CSWS (28). Therefore, a FE-UA more than 12% requires the exclusion of CSWS, before confirming SIAD. Second, FE-UA may be increased by uricosuric drugs like probenecid, sulfinpyrazone, and benzbromarone (29), as well as by losartan, an antagonist of angiotensin II receptors (30). These four drugs should be considered in this context.

FE-urea and S-UA were not influenced by diuretics. However, even though hypouricemia (<4 mg/dl) and increased FE-urea are well-known characteristics of SIAD (16), both parameters demonstrated inferior diagnostic utility in predicting SIAD during diuretic treatment (Fig. 3B, and Tables 2 and 3). Although the mechanism of an increased FE-urea remains unknown, hypouricemia in SIAD is primarily the consequence of a high UA clearance related to decreased tubular UA reabsorption. The limited diagnostic value of both parameters may be explained by the fact that they do not depend only on the volemic state. FE-urea decreases with age (31), varies with the presence of vasopressin (14), and is associated with substantial changes, related to the urinary flow (32). S-UA is also known to be less accurate in the elderly population (33), is enhanced by hypoxemia (34), has a higher serum concentration in men than premenopausal women (35), and is decreased in patients on uricosuric or uricostatic drugs.

In conclusion, we demonstrated that diuretic treatment in hyponatremic patients is frequent. The use of both U-Na and FE-Na for diagnosing SIAD is unreliable in patients on diuretics. FE-UA appears to be a useful tool with a high accuracy for the identification of SIAD in these patients. If these results are replicated in subsequent studies, determination of FE-UA may avoid the withdrawal of diuretics in the diagnostic workup of hyponatremia and replace the 24-h saline infusion test in differentiating SIAD and Na-depleted disorders.

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Address all correspondence and requests for reprints to: Professor Dr. Bruno Allolio, M.D., Endocrinology & Diabetes Unit, Department of Medicine I, University of Wuerzburg, Josef-Schneider-Strasse 2, D-97080 Wuerzburg, Germany. E-mail: allolio_b@medizin.uni-wuerzburg.de.

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