Dissociation between uric acid and urea clearances in the syndrome of inappropriate secretion of antidiuretic hormone related to salt excretion

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(Received 11 September/4 December 1989; accepted 20 December 1989)

SUMMARY
1. Our purpose was to determine why hypouricaemia is more frequently observed than hypouraemia in the syndrome of inappropriate secretion of antidiuretic hormone. We have retrospectively analysed the scores of 35 patients with a chronic form of hyponatraemia related to the syndrome of inappropriate secretion of antidiuretic hormone and studied prospectively six patients.

2. The patients with high fractional excretion of filtered urea (> 55%) presented lower blood urea and lower salt excretion than the patients with normal fractional excretion of filtered urea, despite similar levels of hyponatraemia and of osmotic and uric acid clearances. In six hyponatraemic patients, an increase in salt intake was accompanied by a decrease in fractional excretion of filtered urea. In the syndrome of inappropriate secretion of antidiuretic hormone, the fractional excretion of filtered urea was inversely correlated to the fractional excretion of filtered sodium \( r = -0.66; P < 0.001 \), whereas the fractional excretion of filtered uric acid was not dependent on sodium excretion.

3. Hypouraemia with high fractional excretion of filtered urea in patients with the syndrome of inappropriate secretion of antidiuretic hormone is related to low urinary sodium excretion and thus reflects low sodium intake.

Key words: sodium excretion, syndrome of inappropriate secretion of antidiuretic hormone, urea excretion, uric acid excretion.

Abbreviations: \( \text{FE}_{\text{Cl}} \), \( \text{FE}_{\text{Na}} \), \( \text{FE}_{\text{Osm}} \), \( \text{FE}_{\text{UA}} \) and \( \text{FE}_{\text{Urea}} \), fractional excretion of filtered chloride, sodium, osmotic charge, uric acid and urea, respectively; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

INTRODUCTION
In the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypouricaemia is a typical observation [1]. Hypouraemia is also frequently observed [2]. Both are attributed to an increase in their renal clearances secondary to water retention [3, 4].

In fact, reviewing the scores of patients with hyponatraemia related to SIADH, we observed that many patients presented normal blood urea concentration and hypouraemia. We wanted to study why hypouricaemia was more frequently present than hypouraemia.

Surprisingly, we observed that patients with normal blood urea levels have a normal urea clearance despite high salt excretion, whereas patients with lower urinary salt output exhibit a high urea clearance and hypouraemia.

PATIENTS AND METHODS
We retrospectively analysed the scores of all patients hospitalized with a diagnosis of hyponatraemia related to a SIADH syndrome over a period of 5 years. The following criteria were used to include patients in the series: hyponatraemia with a serum level of less than 130 mmol/l, serum osmolality less than 260 mosmol/kg H₂O associated with inappropriately concentrated urine (urinary osmolality higher than 350 mosmol/kg H₂O in all our patients), absence of oedema or signs of volume depletion and of cardiac or hepatic disease, and normal renal, adrenal and thyroid function [2]. Only patients with an asymptomatic chronic form of the syndrome were studied.
Hyponatraemia was present for more than 1 week. Patients taking drugs known to interfere with uric acid clearance or synthesis were excluded. Only patients with a fractional excretion of filtered uric acid (FEUA) higher than 12%, which is our upper limit of normal, were included [5]. Only three patients presented normal FEUA, and these were not included in the study. Thirty-five patients with asymptomatic hyponatraemia were investigated (mean age ± sd: 52 ± 8 years). Fifteen patients presented the syndrome secondary to cancer (10 oat-cell carcinoma), three to pulmonary tuberculosis, seventeen to various brain diseases (three tuberculosus meningitis, four brain tumours, three subdural haematomas, seven cortical atrophy). All these patients were on a standard hospital diet with no control of salt intake.

Water restriction increased serum sodium concentration in all our patients. The fractional excretions of filtered urea (FEurea), sodium (FENa), chloride (FECI) and osmotic charge (FEOsm) (in %) were calculated as the (urine/serum) concentration of urea, sodium, chloride and osmolality multiplied by the (serum/urine) concentration of creatinine multiplied by 100. These values were obtained in the morning after an overnight fast.

Urine was collected between 08.00 and 10.00 hours, the patients only standing up for voiding. Blood samples were taken at 09.00 hours. In 26 of these patients, the FEUA was simultaneously obtained. The same determinations were performed in a control group of 17 normal subjects of similar age, studied in the same way. In six additional patients on the normal hospital diet (four with oat-cell carcinoma, one with tuberculosis meningitis, one with cortical atrophy), sodium intake was increased by 100 to 150 mmol/day and FEurea, FEUA and FENa were again measured after a few days on this regimen.

All serum and chemical measurements were performed in the hospital clinical laboratory. Uric acid was measured by the uricase method [6].

The values are presented as means ± sd. Statistical analysis of the results was performed by means of Student’s t-test, paired t-test and linear regression.

Table 1. Data in control subjects and in patients with hyponatraemia related to SIADH with normal (group I) and high (group II) FEurea.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 15)</th>
<th>Group II (n = 11)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Serum Na⁺ (mmol/l)</td>
<td>135–145</td>
<td>125.5 ± 4.1</td>
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<tr>
<td>Serum uric acid (mg/100 ml)</td>
<td>2.5–7.5</td>
<td>2.6 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Serum urea (mmol/l)</td>
<td>3.5–6</td>
<td>4.4 ± 1</td>
<td></td>
</tr>
<tr>
<td>Ccr (ml/min)</td>
<td>50–160</td>
<td>109 ± 28</td>
<td></td>
</tr>
<tr>
<td>FEurea (%)</td>
<td>25–55</td>
<td>41.4 ± 8.0</td>
<td></td>
</tr>
<tr>
<td>FEUA (%)</td>
<td>3.5–11.9</td>
<td>20.0 ± 7.1</td>
<td></td>
</tr>
<tr>
<td>V/CCr × 100 (%)</td>
<td>0.25–1</td>
<td>0.77 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>FEOsm (%)</td>
<td>0.80–2.7</td>
<td>2.0 ± 0.55</td>
<td></td>
</tr>
<tr>
<td>Urinary urea as a % of total solutes</td>
<td>500–1030</td>
<td>661 ± 91</td>
<td></td>
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<tr>
<td>FENa + FECI (%)</td>
<td>0.65–2.8</td>
<td>2.08 ± 0.87</td>
<td></td>
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<tr>
<td>FENa (%)</td>
<td>0.23–1.1</td>
<td>0.88 ± 0.30</td>
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Abbreviations: V, urine volume; Ccr, creatinine clearance; NS, not significant.
Urea and inappropriate secretion of antidiuretic hormone

vs 49.8 ± 13.6; P < 0.001) in the group with a high FEUrea (group II). FENa and FECr were significantly higher in the group with normal FEUrea (group I). Blood urea concentration was inversely correlated to FEUrea (r = 0.41, n = 26; P < 0.05) in the patients but not in the control subjects (r = -0.15). Fig. 1 shows the effects of urinary flow rate on FEUrea in the control subjects (indirectly expressed as the urinary creatinine/plasma creatinine ratio; r = -0.61; P < 0.01). The patients in group II presented clearly higher values than those in group I, despite having a similar urinary flow rate. Fig. 2 demonstrates that FEUrea is inversely correlated to FENa (r = -0.66; P < 0.001) in our 35 patients, whereas no significant correlation was observed in the control subjects (r = 0.45; P < 0.10). There was no correlation between FEUA and FENa (r = 0.29, data not shown). In our study we included only patients with a high FEUrea because this is a well-known feature of hypotraemia related to SIADH. In fact, only three patients with low blood urea levels presented a normal FEUrea in our retrospective study and otherwise all exhibited the characteristics of SIADH. If these three patients were included, the same observations were still made: FEUrea was inversely correlated to FENa (r = -0.69, n = 38; P < 0.001), whereas no correlation was observed between FEUA and FENa (r = 0.22; not significant). Table 2 shows the changes in FEUrea and FENa measured in six patients in whom salt intake was increased. The serum sodium concentration and urinary flow did not change significantly during the two regimens but FEUrea decreased when FENa increased, whereas uric acid clearance did not change.

DISCUSSION

Hypouraemia in SIADH could result from decreased production and/or increased clearance of urea [3]. We observed that in SIADH urea clearance is highly dependent on salt excretion. It is generally accepted that in humans the filtered urea not excreted in the urine is passively reabsorbed throughout the tubule [7], although active secretion and reabsorption may occur by active transport [8-10]. The magnitude of this reabsorption may be altered by changes in urine flow rate [11], glomerular filtration rate [12], dietary protein intake [13] and effective intravascular volume [14]. In our two groups of SIADH patients, the difference in FEUrea cannot be explained by a difference in urine flow rate, as they were identical. The increased urea clearance in group II could not be explained by an increased glomerular filtration rate frequently observed in patients presenting with SIADH [2, 15] because of their inappropriately high FEUrea. Our patients were not strictly controlled for protein and salt intakes, but if their protein intake had been low we would have expected a decrease in FEUrea [13] and not the increase that we observed in the patients with low salt excretion. As expected, the absolute excretion of urea did not differ between group I (0.20 mmol/min) and group II (0.22 mmol/min). This suggests that urea production and protein intake were similar in both groups. It became evident, when we separated the patients on the basis of their FEUrea, that salt excretion was different in the two groups. It is important to note that osmotic clearances in the two groups were not different from our control subjects; this has been shown in animals during the chronic phase of SIADH [16]. In spite of the similar osmotic clearances, the patients with high salt excretion presented a lower percentage of urea in the total urine solute con-

Table 2. Effect of high salt intake (phase II) on FEUrea in six patients with SIADH, measured during similar hypotraemia and urine flow rate

<table>
<thead>
<tr>
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<th>Phase I</th>
<th>Phase II</th>
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<tbody>
<tr>
<td>Serum urea (mmol/l)</td>
<td>3.3 ± 1.0</td>
<td>4.0 ± 1.2</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Serum Na⁺ (mmol/l)</td>
<td>123.8 ± 3.7</td>
<td>124.1 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Serum uric acid (mg/100 ml)</td>
<td>2.6 ± 0.7</td>
<td>2.5 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>V/Cr × 100 (%)</td>
<td>0.65 ± 0.13</td>
<td>0.76 ± 0.20</td>
<td>NS</td>
</tr>
<tr>
<td>FEUA (%)</td>
<td>17.5 ± 5.3</td>
<td>20 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>FEUrea (%)</td>
<td>63.8 ± 6.3</td>
<td>43.1 ± 8.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>0.34 ± 0.16</td>
<td>0.9 ± 0.33</td>
<td>&lt;0.01</td>
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</table>
centration and a lower FE\textsubscript{Urea} with higher blood urea concentration than the patients with lower salt excretion (group II).

In SIADH, in the steady state, it is known that salt excretion is strictly dependent on salt intake [2]. Salt excretion is higher than salt intake during the first days when hyponatraemia develops and only when water intake is high [2, 17, 18]; later, salt excretion depends only on salt intake. In our patients hyponatraemia was chronic and all measurements were made after at least 1 week of observation, so that the difference in salt excretion between the two groups could not be explained by measurements made during the developing phase of hyponatraemia for the first group and later for the second.

Another origin of high salt excretion in our group I patients which has to be excluded is 'cerebral salt wasting syndrome' [19-21]. This is unlikely because all our patients increased their serum sodium concentration by simple water restriction and, in at least six patients (see Table 2), the increase in salt intake induced an increase in FE\textsubscript{Na}, without changing the serum sodium concentration but decreasing FE\textsubscript{Urea}. In addition, cerebral disease was no more frequent in one group than in the other. In fact, these variations in salt excretion reflect different salt intakes among patients. For some patients of group I this was related to a spontaneously high salt intake, whereas in others salt supplementation was performed orally or by an intravenous route. In normal normovolaemic man variation in salt intake is not known to influence notably urea clearance [7], although recently a decrease in urea excretion has been reported in normal man submitted to a high salt diet and having free access to water [22]. McCance & Young [23] have shown, in normal man studied during water restriction, that maximum urine concentration of urea and chlorine or sodium could not be obtained simultaneously.

In SIADH the subject is permanently in antidiuresis so that sodium concentration is also inversely correlated to urea concentration [24], but the high correlation observed between FE\textsubscript{Na} and FE\textsubscript{Urea} is a new observation. If a low FE\textsubscript{Na} is presumed to be secondary to a decrease in the 'effective vascular volume' this situation should normally be associated with a low FE\textsubscript{Urea} and a trend to uraemia [14]. A normal [25] or increased [2] 'volacema' combined with an antidiuresis is probably necessary to observe this inverse correlation. In our two groups of patients, serum uric acid concentration and FE\textsubscript{Ura} were identical, which probably reflects a similar degree of volume expansion. It is known that expansion induced by saline infusion in humans increases the clearances of uric acid, and that this is only related to the infused volume and not to the sodium load or serum sodium concentration [26]. Our study shows that urea clearance is less sensitive than uric acid clearance as an indirect measure of effective volacema. It has been shown in a study of SIADH in man [24, 27, 28], and recently in animals [29], that treatment with urea could decrease salt excretion. The cause of the sodium-sparing effect of urea may be an increased osmolality of the inner medulla [29]. In SIADH an increased intake of sodium is urinary urea sparing.

ACKNOWLEDGMENTS

This work was supported by a grant from the Fonds National de la Recherche Scientifique (F.N.R.S.) (1.5.228.90F) and a grant from the Ministère de la Politique Scientifique (Actions concertées).

REFERENCES