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Original article

Plasma arginine vasopressin and atrial natriuretic peptide concentration in patients with hyponatremia at diagnosis and following treatment

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Abstract

Background: Much evidence for arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) in the pathogenesis of hyponatremia in humans is based on single measurements. To study the roles of AVP and ANP in the pathogenesis and recovery of hyponatremia, sequential measurements of ANP and AVP were taken during treatment in a group of hyponatremic patients with different etiologies.
Methods: Consecutive adult patients with hyponatremia (serum Na <130 mmol/l) and healthy controls were studied. Volume status was determined by clinical and laboratory criteria. Plasma AVP and ANP, fractional sodium excretion, and urine osmolality were determined daily until serum Na was above 135 mmol/l or for at most 7 days.
Results: A total of 16 controls and 40 hyponatremic patients (12 normovolemic, 9 hypervolemic, and 19 hypovolemic) were studied. Patients' plasma AVP on the first day [1.0 (0.3–2.3) ng/l] and on the last day [1.1 (0.3–2.5) ng/l] of the study did not differ from that of controls [0.7 (0.5–1.0) ng/l]. Serum sodium concentration increased significantly in patients between the first and the last day. Patients had significantly lower ANP concentrations, both on the first day [25 (15–46) ng/l] and on the last day [29 (17–46) ng/l], than controls [41 (28–51) ng/l]. Plasma AVP was elevated relative to serum osmolality on the first day and to a lesser extent on the last day of the study.
Conclusions: AVP is inappropriately high in a majority of hyponatremic patients. Plasma AVP and ANP concentrations do not change during treatment in hyponatremic patients despite a significant increase in serum osmolality. A low ANP concentration in clinically normovolemic and hypovolemic patients indicates volume depletion, which may lead to baroreceptor-stimulated AVP secretion.

Keywords: Hyponatremia; Pathogenesis; Longitudinal cohort study; Arginine vasopressin; Atrial natriuretic factor

1. Introduction

Hyponatremia is a common electrolyte disorder in hospitalized patients [1,2]. In a majority of cases, hyponatremia is caused by limited renal free water clearance [3–5]. At least two hormones are involved in the pathogenesis of hyponatremia: the antidiuretic hormone arginine vasopressin (AVP) and atrial natriuretic peptide (ANP). Renal water regulation by AVP is currently understood at the molecular level since the discovery of vasopressin 2 receptors and aquaporin water channels [6]. Aquaporin-2 water channels in renal collecting ducts mediate AVP activity. AVP is thought to be one of the causal factors of hyponatremia, based on the finding of non-suppressed levels of AVP despite serum hypo-osmolality in a majority of cases [1,7–9]. ANP is predominantly secreted in cardiac atria in response to atrial distension. ANP exerts its effects by binding to specific membrane-bound receptors. In the kidney, ANP increases glomerular filtration rate and inhibits sodium reabsorption directly in the collecting duct and indirectly by inhibiting aldosterone secretion. One of the actions of ANP is regulation of volume homeostasis and, therefore, indirectly of water homeostasis [10]. ANP has also been implicated as a causative factor in the pathogenesis of cerebral salt wasting syndrome

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(CSW) [11,12]. CSW is characterized by renal sodium loss leading to extracellular volume depletion. This is followed by compensatory water retention and hyponatremia [11–13].

Much evidence for the roles of AVP and ANP in the pathogenesis of hyponatremia in humans is based on single hormone measurements performed after hyponatremia is diagnosed [1,7–9,14–16]. In patients with the syndrome of antidiuretic hormone secretion (SIADH), sequential changes in plasma AVP concentration induced by hypertonic saline infusion showed different aberrant patterns of vasopressin response, indicating osmoregulatory dysfunction [7,17]. To disentangle the roles of AVP and ANP in the pathogenesis and recovery of hyponatremia in a group of patients with hyponatremia of different etiologies, sequential observational measurements may be helpful. As this is rather impossible before the onset of hyponatremia, we turned our attention to the course of plasma AVP and ANP concentrations following the diagnosis of hyponatremia and recovery. We thought that a 'sequence in reverse' might shed more light on the roles of AVP and ANP in the pathogenesis of hyponatremia. In the literature, little is known about the course of plasma AVP and ANP concentrations in hyponatremia following diagnosis, except for certain disorders like subarachnoid hemorrhage [18–21]. We took daily measurements of plasma AVP and ANP concentrations in hospitalized patients with hyponatremia of different etiologies. Measurements were started when hyponatremia was diagnosed. Patients were studied at most for 7 days after diagnosis. In order to compare AVP and ANP concentrations from hyponatremic patients with AVP and ANP concentrations in physiological conditions (normovolemia and normal plasma osmolality), we also measured plasma AVP and ANP concentrations in a control group consisting of age- and sex-matched healthy volunteers.

2. Patients and methods

2.1. Patients and controls

We studied consecutive adult hospitalized patients with hyponatremia at Leiden University Medical Center. Hyponatremia was defined as a serum sodium concentration of 130 mmol/l or less. We included patients from the Department of Internal Medicine (mean number of hospitalized patients per day: 79 patients) and from the Department of Neurosurgery (25 patients). These departments were selected because hyponatremia is a frequently occurring electrolyte disorder in these departments. Initial case findings were based on sodium concentration measurements. Sodium measurements were taken if ordered by the physicians responsible for the patients at the departments. Part of the population at risk did not have serum sodium concentration measured and, consequently, hyponatremia could not be identified in these patients. Lists of in-hospital patients from the abovementioned departments who had a serum sodium concentration of 130 mmol/l or less were drawn every day from laboratory computer reports at 8.30 a.m. and at 4.30 p.m. Patients who were hyponatremic on admission as well as patients who developed hyponatremia during admission were included in the study. Patients were excluded if treatment for hyponatremia had already been started before entering the study.

The study protocol was approved by the ethics committee of the Leiden University Medical Center. After permission of the attending physician was obtained, informed consent was obtained from the patient or close relatives. Patients were studied until serum sodium concentration normalized (defined as serum sodium concentration $\geq$135 mmol/l) and at most for 7 days if serum sodium concentration remained below 135 mmol/l for more than a week. Sixteen age- and sex-matched healthy volunteers were recruited to serve as a control group. Blood samples were taken from these volunteers at 8:00 a.m. after an hour of rest in the supine position.

2.2. Clinical assessment and record review

Medical records of the patients were reviewed. Special attention was paid to the reason for admission, date of admission, relevant medical history, disease course during hospital stay, medication, dietary prescriptions, the quantity and type of parenteral fluids received the day before inclusion, and urinary production if recorded previously. An assessment of the volume status was made using physical examination and laboratory-based findings (see below). At physical examination, special attention was paid to the humidity of mucous membranes, skin turgor, visual assessment of external jugular venous pressure, weight course, the presence of edema, hydrothorax, ascites, and blood pressure in the supine position and, if possible, in the upright position. Orthostatic hypotension was defined as a drop in systolic blood pressure of at least 20 mm Hg after 2 min in the upright position compared to the supine position. Changes in hematocrit, urea, uric acid, and creatinine concentration were taken into account in order to estimate the volume status.

2.3. Laboratory measurements

In sera, sodium, potassium, chloride, bicarbonate, urea, creatinine, uric acid, albumin, and glucose concentrations were measured. In urine, sodium concentrations and osmolality were measured. For all measurements, a Hitachi 747 analyzer (Boehringer Mannheim, FRG) was used. Hematocrit was determined using a Coulter Counter (Coulter Electronics Inc., Hialeah, Florida, USA). Urinary osmolality was measured using Osmostat (Osmostat, OS-6030, Menarini, Florence, Italy). Effective serum osmolality was calculated using the formula: 2 × serum sodium concentration (mmol/l) [22]. Fractional sodium excretion was calculated using the formula: (urine sodium concentration (mmol/l) × serum creatinine concentration (μmol/l)) × 100/(serum sodium concentration (mmol/l) × urine creatinine concentration (μmol/l) (%) [22].