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CT-pro-AVP as a tool for assessment of intravascular volume depletion in severe hyponatremia

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ABSTRACT

Background: Assessment of volume status is essential to best manage hyponatremic patients but is not always accurate in clinical practice. The aim of this study was to evaluate the reliability of C-terminal portion of pro-arginine-vasopressin (CT-pro-AVP), a surrogate biomarker of vasopressin release, in assessing intravascular volume (IVV) depletion in hypoosmolar hyponatremic patients.

Methods: Plasma CT-pro-AVP and urea-to-creatinine ratio (Ur/Cr) were performed in 131 hospitalized patients presenting chronic severe hypoosmolar hyponatremia. At hospital discharge, their IVV was evaluated regardless of CT-pro-AVP concentrations. All patients were then classified as decreased or as normal/expanded IVV group.

Results: Plasma CT-pro-AVP levels were higher in patients with decreased IVV (34.6 vs. 11.3 pmol/L, $p < 0.001$) and exhibited a reliable performance for assessment of decreased IVV (ROC AUC at 0.717 [95% CI 0.629–0.805]). The combination of CT-pro-AVP and Ur/Cr resulted in an improved ROC AUC up to 0.787 (95% CI 0.709–0.866).

Conclusions: Our findings support the hypothesis that CT-pro-AVP plasma level may reflect IVV and would be a tool for its assessment. This performance has been magnified by its combination with Ur/Cr. A dual-marker strategy may help clinicians to optimize the management of severe hyponatremia especially in case of confusing clinical presentations.

Introduction

Hyponatremia, defined as a plasma sodium concentration of less than 135 mmol/L, occurs frequently in hospitalized patients and has prognostic implications. A recent study of 13,276 Intensive Care Unit patients reported the prevalence of hyponatremia at 12.9% and of severe hyponatremia (sodium level ≤125 mmol/L) at 5.9%. Hospital mortality reached more than 40% among these severe patients [1]. This mortality was not only due to the associated cause of hyponatremia but also to its therapeutic management. Indeed, the evaluation of hyponatremia is not always accurate because of the lack of constant and specific signs. In the study of Hula et al., significant management errors were reported in 33% of hyponatremia and conferred a higher mortality [2].

Hypotonic hyponatremia is an imbalance of water and sodium homeostasis induced by a proportional excess of total body water relative to the total body sodium [3–5]. The assessment of effective intravascular volume (IVV) is a main condition to decide appropriate treatment as rehydration [5]. The routine approach consists of patient's history and physical examination but the assessment of volume status is not always reliable and the distinction between total extracellular volume (ECV) and effective IVV status is difficult in clinical practice [4–6]. In fact, as seen in Fig. 1, an expanded ECV could be associated with a decreased IVV, such as congestive heart failure, hepatic cirrhosis, and nephrotic syndrome, or with an expanded IVV such as renal failure.

Arginine vasopressin (AVP) is one of the key hormones of water homeostasis. Urine sodium concentration and osmolality are usually measured to assess its activity. The suppression of AVP activity by increased IVV generally results in urine osmolality <100 mOsm/kg [5], while its stimulation by hypovolemia increases urine osmolality above serum osmolality. Consequently, urine osmolalities between 100 mOsm/kg and the level of plasma osmolality represent a gray area in which it is difficult to precisely assess fluid status [5,7]. However, urine analysis is influenced by diuretics and urine samples are often difficult to be

Abbreviations: AVP, arginine vasopressin; CT-pro-AVP, C-terminal pro-arginine vasopressin; ECV, extracellular volume; FENa, fractional sodium excretion; IVV, intravascular volume; Ur/Cr, urea-to-creatinine ratio.

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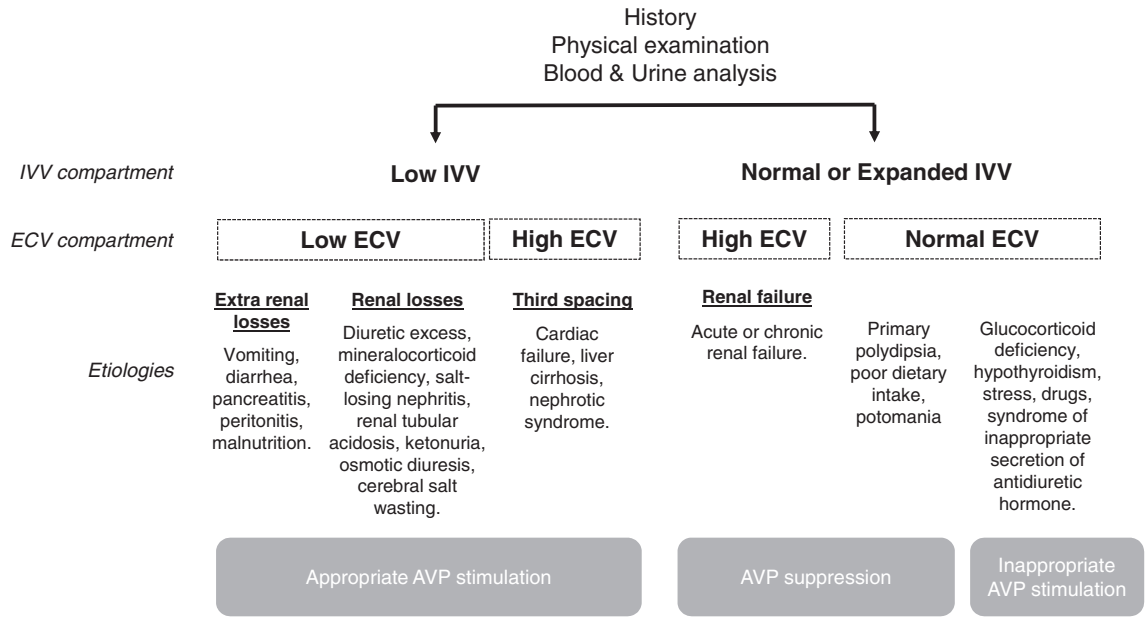

Fig. 1. Intracellular and extracellular volume fluid status depending on mechanisms of subsequent hyponatremia. Abbreviations: IVV, intracellular fluid volume; ECV, extracellular fluid volume; and AVP, arginine vasopressin.

taken, especially in emergency units. Direct measurement of endogenous AVP in plasma could be therefore useful to assess IVV [8,9], but it is not suitable for use in clinical practice due to the binding of AVP to platelets and its unstability in isolated plasma [10,11]. In contrast, the C-terminal portion of provasopressin (CT-pro-AVP), which is co-secreted with AVP, is much easier to quantify. CT-pro-AVP is a 39-amino acid glycopeptide that may have a role during the intracellular processing of provasopressin. It is produced together with AVP in an equimolar ratio and has similar kinetics as described for AVP. CT-pro-AVP is now frequently used as a surrogate marker for AVP secretion in clinical studies [8–12].

The aim of this study was therefore to evaluate the reliability of the plasma CT-pro-AVP concentration in assessing IVV status in hypoosmolar hyponatremic patients. Our hypothesis was that CT-pro-AVP may reflect IVV and should help for the management of severe hyponatremia. If IVV is decreased, AVP levels, and so CT-pro-AVP levels, should dramatically increase much more than in the case of syndrome of inappropriate secretion of antidiuretic hormone or in the case of expanded IVV (in which CT-pro-AVP concentrations should decrease). We sought also to compare it to routine biological parameters used to diagnosis hyponatremia in clinical settings including the ratio of plasma urea to plasma creatinine [13–15].

Patients and methods

Study design and population

All hospitalized patients presenting hyponatremia at the University Hospital of Montpellier between July 2012 and January 2013 were screened for the study. Inclusion criteria included an age older than 18 years and a chronic (≥48 h) severe hypoosmolar hyponatremia defined as a plasma sodium concentration less than 125 mmol/L and a plasma osmolality less than 275 mOsm/kg. Patients with renal failure with an estimated glomerular filtration rate <15 mL/min/1.73 m^2 were not eligible. The study was performed according to the principles of the Declaration of Helsinki and was approved by the local ethics committee. Demographic, clinical and laboratory data were collected during hospitalization. All laboratory values (plasma glucose, creatinine, urea, urine sodium excretion and urine osmolality) were collected upon the occurrence of hypoosmolar hyponatremia within first sodium measurement.

Diagnostic criteria and classification

The assessment of the ECV, IVV and body sodium compartments was reinterpreted after the discharge of patients by three trained investigators (KK, JPC, SJ) using weight (at admission and at discharge), clinical picture (orthostatic hypotension, clinical signs of dehydration, history), therapeutic management (including saline loads), response to treatment, biology (urinary sodium concentration), and final diagnosis according to consensus-based clinical recommendations [4,5]. All patients were classified into one of the two categories depending on IVV status as shown in Fig. 1: 1) Decreased IVV and 2) Normal or expanded IVV. The investigators were blinded to results of plasma CT-pro-AVP measurements.

Laboratory assessment

Blood samples were collected into lithium heparin tubes and were processed at the clinical chemistry laboratory. A plasma aliquot was stored at −20 °C for later analysis. Routine laboratory parameters were measured by automated Cobas 8000 analyzer (Roche Diagnostics, Meylan, France). Urine and plasma samples were analyzed using ion-selective electrodes for sodium. The glutamate dehydrogenase and hexokinase method were used for the determination of plasma urea and glucose levels and IDMS-traceable creatinine enzymatic assays was used for plasma creatinine measurement. Osmolality was measured with an osmometer by means of freezing point depression (ThermoFisher Scientific, Clichy, France). The effective osmolality was obtained as serum osmolality less serum urea level in millimoles per liters [16,17]. Plasma urea-to-creatinine ratio was calculated by the formula: (*urea* (mmol/L) / *creatinine* (μmol/L)) × 10^3 [13–15]. The fractional sodium excretion (FENa) was calculated by the formula: 100 × [*urinary sodium* (mmol/L) × (*plasma creatinine* (μmol/L) / 1000)] / [*plasma sodium* (mmol/L) × *urinary creatinine* (mmol/L)].

The CT-pro-AVP was performed from frozen lithium heparin plasma samples using the CT-pro-AVP assay on the Kryptor Compact Plus systems (Thermofisher Scientific, Clichy, France) which allows a time to result of 18 min as previously described [18]. For values between 3 and 16 pmol/L, within- and between-assay imprecision ranged from 2.4% to 11.3% and from 3.9% to 10.2%, respectively. The LoD was 1.90 pmol/L in our conditions.