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Mini Review article

Hypotonic Hyponatraemia and Diuretic Therapy: A Challenging Diagnostic Dilemma

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Abstract

Nearly thirty% of hospitalized patients present an electrolyte imbalance such as hyponatremia (serum sodium <135 mEq/L) while a severe grade (<125 mEq/L) is detected in up to 2% of inpatients. Syndrome of inappropriate antidiuresis (SIAD) represents the most common etiology affecting nearly 35% of these hyponatremic inpatients.

Keywords: hyponatremia; SIAD; SIADH; diuretics; thiazide; FEUA; FEK

Nearly thirty% of hospitalized patients present an electrolyte imbalance such as hyponatremia (serum sodium <135 mEq/L) while a severe grade (<125 mEq/L) is detected in up to 2% of inpatients. Syndrome of inappropriate antidiuresis (SIAD) represents the most common etiology affecting nearly 35% of these hyponatremic inpatients [1,2]. Different causes of SIAD are recognized such as drugs, malignancies, neurologic and pulmonary disorders [3]. The classical criteria of Schwartz and Barter are used to make diagnosis (Table 1, 4). International guidelines suggest different algorithms to support the differential diagnosis of hypotonic hyponatremia [3, 5]. Unfortunately, the bias of these diagnostic flowcharts is coming from a wrong clinical assessment of the volemic status, especially during diuretic treatment [6] with a low diagnostic sensitivity and specifity [7]. Thus, The European guideline committee suggest an algorithm that prioritizes urine osmolality and urine sodium concentration over volume status (fig.1, 3). Anyway, three different caveats on urine Na interpretation should be underlined: [1] a low sodium diet determines low urine sodium, [2] the use of diuretics increases the urine sodium, [3] the presence of chronic kidney disease reduces the possibility to reabsorb sodium. Then, the urine sodium could be increased >30 mEq/L, especially in older people, also in presence of a hypovolemic status and fractional excretion of sodium (FENa<0.5%) is a more reliable test but, unfortunately, up to 42% od SIAD patients present reduced values [8].

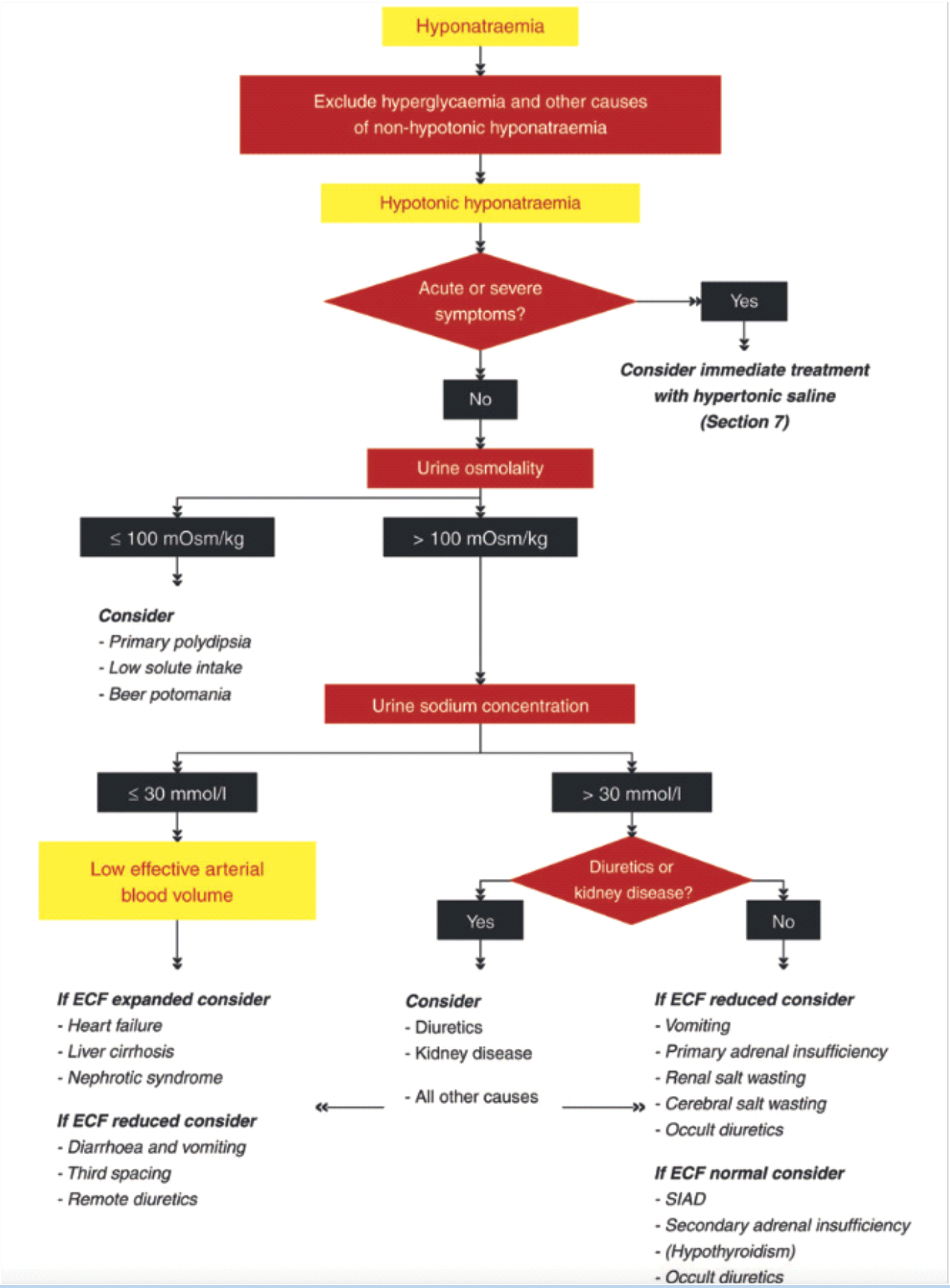


Figure 1: *Diagnostic algorithm for hyponatremia (from Spasovsky et al. reference 3)*

The use of diuretic drugs such as thiazide, potassium-sparing and loop diuretics, is worldwide diffused to treat congestive heart failure, chronic renal failure, cirrhosis and arterial hypertension. These drugs, blocking ion-cotransporters at different sites, induce both inhibitions of tubular Na reabsorption and increase of urine Na and water excretion with a relative hypovolemic status.

Usually, thiazide drugs are more involved in hyponatremia onset than loop-diuretics where furosemide, decreasing the osmolality of renal medulla and the urine concentration, induces a hyponatremic status only at high dose or in association with potassium sparing-diuretics [9].

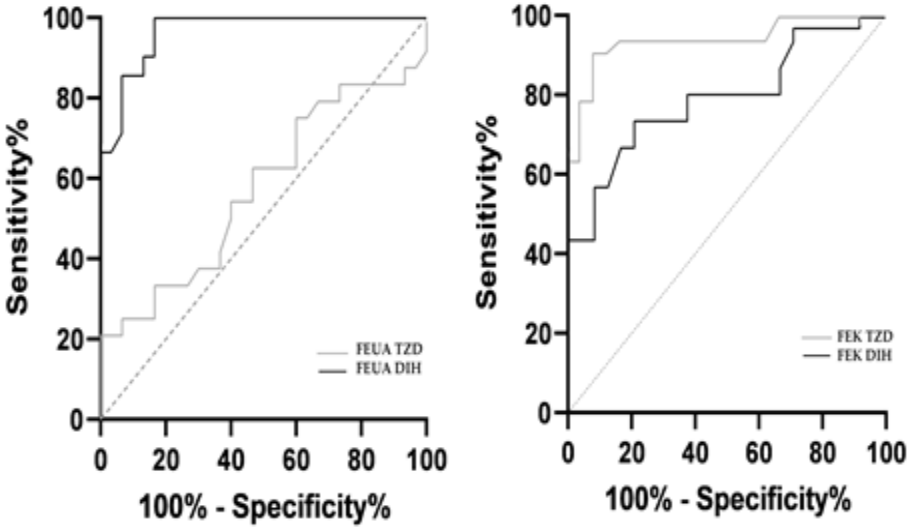
A substantial loss of sodium and body weight have waited during diuretic treatment but thiazide-treated hyponatremic patients show an increased body weight suggesting different causes [10]. Water retention from both an increase of arginine vasopressin activity and/or upregulation of aquaporin-2 expression has been demonstrated [11]. Moreover, hypokalemia, a frequent hallmark of thiazide-treated patients, increases the volume receptor release of vasopressin [12]. Different genetic expressions of specific prostaglandin transporters, in the subset of patients prone to developing hyponatremia, could be involved [13,14]. Then, thiazide drugs increase six-fold the risk of hyponatremia versus non-exposed patients with an estimated incidence of 11% in the geriatric population [15].

Thus, many clinical trials arbitrarily excluded the diagnosis of SIAD in the presence of diuretic treatment. To make a correct SIAD diagnosis, the usual approach is to withdraw diuretic therapy for up to ten days with a longer hospitalization stay and increased hospital admission costs [16].

A fluid challenge test (2 L/day of isotonic saline solution) has been proposed to exclude mild hypovolemic status discriminating between SIAD and sodium-depleted (SD) patients. In SD is described a typical increase of serum Na (>5 mEq/L) with FENa <0.5% while in SIAD a sharp rise of FENa prevents the rise of serum Na. Anyway, nearly 30% of SIAD patients respond in a confounding way showing a Na increase to fluid challenge test [17]. Moreover, isotonic saline solution may worsen hyponatremia in patients with high urine osmolality (desalination phenomenon).

Recently, further laboratory markers have been proposed to improve the diagnostic approach to hyponatremia. Serum uric acid (UA) is a marker of the volemic status in acute patients considering that renal handling, exclusively in the proximal tubule, is preserved by interferences of the most used diuretics (18). Moreover, the fractional excretion of uric acid (FEUA) value is also a more accurate parameter obtained with a simple blood and urine spot sample avoiding a 24 h urine collection [19]. Beck reported that SIAD patients showed a UA level <4 mg/dl with increased FEUA values [20] dependent on a decrease in tubular reabsorption [21] where urate secretion seems to be appropriate for the level of uricemia [22].

Fenske et al. demonstrated that FEUA value (cut-off value >12%, 86% sensitivity and 100% specificity) could discriminate between SIAD and diuretic-induced hyponatremia. The limit of this study was the low recruited number of patients treated with thiazide therapy (only 7 patients corresponding to 13% of the overall group, [23]. Successively, several observations showed that FEUA was not reduced in thiazide use as in other diuretic-treated populations where the bulk of TIH patients resulted clinically euvolemic resembling SIAD phenotype [24]. To clarify the issue, recent studies, using Receiver Operating Characteristics curve analysis, demonstrated the failing of FEUA parameter to discriminate SIAD vs. SD when treated with thiazide drugs (fig. 2) [25].



AUC: Area under the curve (95% confidence interval).

FEUA SIAD/DIH: AUC 0.96 (0.92-1.0) ; SIAD/TZD: AUC 0.58 (0.41-0.73);

FEK SIAD/DIH: AUC 0.79 (0.67-0.91); SIAD/TZD: AUC 0.94 (0.87-1.0)

Figure 2: *ROC curves analysis of FEUA (left) and FEK (right) values of SIAD vs. Diuretic Induced Hyponatremia (DIH) and Thiazide-treated (TZD) groups. (from Bassi et al. Reference 25)*

A further tool has been proposed to improve the diagnosis of hyponatremia such as fractional excretion of potassium (FEK), a marker typically increased in diuretic therapy or Renal Salt Wasting (RSW) syndrome. A recent study involving a small cohort of hyponatremic

patients showed that normal FEK value were found in SIAD versus increased value in diuretic treated patients comprising the thiazide treatment. Thus, the combined pattern of FEUA/FEK parameters may discriminate between SIAD and overall diuretic treated patients in hypotonic hyponatremia (fig. 3, 26).

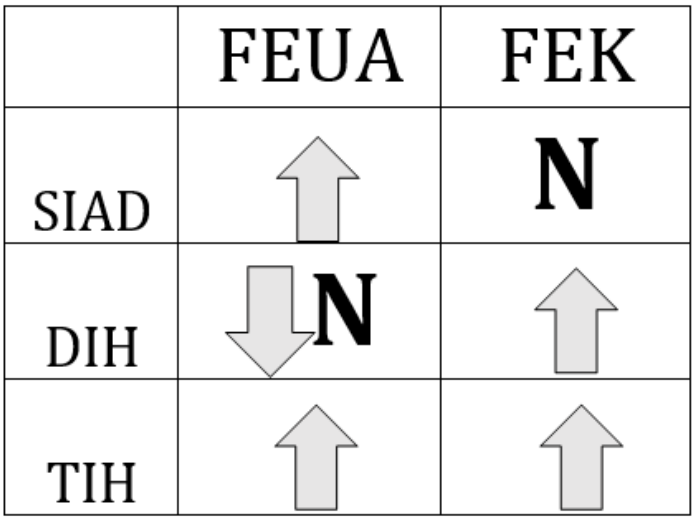


Figure 3: *patterns of combination of investigated parameters FEUA/FEK in the different causes of hypotonic hyponatremia. (Modified from Bassi et al. reference 26)*

Moreover, SIAD patients treated with diuretic therapy presented normal and not increased FEK values suggesting that the increased glomerular filtration rate from extracellular fluid volume expansion induced an elevated filtered potassium (K) in the glomerulus. Furthermore, the euvolemic/mild hypervolemic status in SIAD decreased the activity of the renin/angiotensin/aldosterone axis reducing K lost at the renal tubules [26].

The net result of an increased glomerular K filtration and reduced tubular K excretion justified the normal FEK values found in SIAD.

A further consideration from this study is that the normal FEK values found in SIAD patients confirmed the hypothesis that RSW is a rare cause of hypotonic hyponatremia.

In conclusion, new markers such as the pattern of association of FEK/FEUA values, could be considered in the differential diagnosis of hyponatremia. Further investigations involving larger cohorts of patients will be necessary to modify the diagnostic flowcharts in hypotonic hyponatremia of patients treated with diuretics.

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