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Review

HYPONATREMIA IN PREDIALYSIS HOSPITALIZED PATIENTS: AN UPDATE ON CLINICAL DATA AND MANAGEMENT

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REZUMAT

Hiponatremia la pacienții spitalizați în faza predializă: update privind aspectele clinice și managementul

Hiponatremia este frecvent întâlnită la pacienții spitalizați. În funcție de tonicitatea măsurată a plasmei, hiponatremia poate fi hipotonă, izotonă sau hipertonă. În funcție de statusul volemic, hiponatremia poate fi hipervolemică, izovolemică sau hipovolemică. În insuficiența renală cronică, aportul de apă depășește excreția și are ca rezultat hiponatremia hipervolemică. Hiponatremia în insuficiența renală cronică are particularități fiziopatologice, clinice și de management.

Cuvinte cheie: hiponatremie, boală renală cronică, management

ABSTRACT

Hyponatremia is frequently encountered in hospitalized patients. According to the measured plasma tonicity, hyponatremia could be hypotonic, isotonic or hypertonic. According to the volemic status hyponatremia could be hypervolemic, euvolemic, or hypovolemic. In renal failure the water intake exceeds the excretion and the result is hypervolemic hyponatremia. Hyponatremia in renal failure implies some pathophysiological, clinical and management particularities.

Key words: hyponatremia, chronic kidney disease, management

INTRODUCTION

Hyponatremia, with an incidence of 15 – 22%, is considered when serum sodium levels are < 135 mEq/L (in institutionalized geriatric patients, in 1 – 4% to 7 – 53% cases there have been reported values below 130 mEq/L) [1-3]. Additionally, according to expert panel recommendations the frequency of hyponatremia in hospitalized patients depends on the detected level of hyponatremia [2]. This special

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Table 1. Hyponatremia classification

	Hypotonic < 285 mOsm/kg	
hypovolemia	*euvolemia* (water intoxication)	*hypervolemia*
• extrarenal fluid loss (e.g.: gastrointestinal – vomiting, diarrhea; cutaneous; respiratory) – urinary Na^+ < 10 mEq/L • renal fluid loss (e.g.: excessive diuretics administration, salt-losing nephropathy, adrenal insufficiency) – urinary Na^+ > 20 mEq/L	• renal failure • endocrine disorders (e.g.: syndrome of inappropriate ADH secretion, hypothyroidism, pregnancy) [10-15] • tumors (e.g.: small cell lung cancer) [16-18] • significant physical exercises (e.g.: marathon) • drug intoxication (e.g.: ecstasy abuse) [19-29] • severe psychiatric illnesses (e.g.: primary polydipsia) [30] • low dietary intake (e.g.: beer drinkers, malnourished patients) [31-33]	• nephrotic syndrome • hepatic cirrhosis • heart failure • acute or chronic renal impairment
	Isotonic 285 – 295 mOsm/kg	
• after isotonic non-sodium solution infusion (e.g.: during transurethral prostate or bladder resection - transurethral resection syndrome, hysteroscopy, laparoscopy) • pseudohyponatremia – induced by marked hyperlipidemia (triglycerides > 1500 mg/dL) and –proteinemia (serum protein > 10g/dL) [34,35] • following excessive isotonic fluid infusion (5%) (e.g.: glucose, mannitol)		
	Hypertonic > 295 mOsm/kg	
• marked hyperglycemia [36]		
• after excessive hypertonic solution infusion (> 10%) (e.g.: glucose, mannitol, ethanol, glycerol)		

* *Modified after: Verzan C. Tulburările homeostaziei apei și eletroliților. In: Ursea N (editor). Tratat de Nefrologie. 2nd Ed. Bucharest: Editura Fundației Române a Rinichiului, 2006; p. 503-546.*

* *Modified after: Sterns RH. Causes of hyponatremia in adults. UpToDate. 2013; http://www.uptodate.com.ezproxy.umf.ro/contents/causes-of-hyponatremia-in-adults.com.*

* *Modifed after: http://emedicine.medscape.com/article/242166-overview; accessed August 2014.*

condition is highly important to be detected on time because it represents a recognized risk factor of morbidity and mortality, even in asymptomatic patients [1]. Furthermore, it was noticed that a swift correction can induce severe neurological disorders and even death [1]. Therefore, for an adequate treatment management (prophylaxis and therapy) is vital for understanding hyponatremia main causes and the incriminated pathophysiological mechanisms [1].

Clinical importance of the pathophysiological particularities

Hyponatremia is important because it is in close relationship with plasma osmolality. Plasma osmolality (Posm) can be measured directly or calculated by the following expression [2,3]:

$$Posm = (2x\ serum\ [Na+] + glucose/18 + BUN/2.8)$$

Blood urea nitrogen (BUN) and glucose are expressed in milligrams per deciliter (mg/dL) and serum sodium [Na+] in milliequivalents per liter (mEq/L) [2,3].

Depending on the plasma tonicity, hyponatremia could appear in the following conditions: hypotonic plasma (< 280 mOsm/kg H_2O) as in syndrome of inappropriate antidiuretic hormone secretion, cirrhosis and heart failure; isotonic plasma (280-295 mOsm/kg H_2O) as in hyperglycemia, hyperlipidemia and hyperproteinemia; hypertonic plasma (> 295 mOsm/kg H_2O) as in severe hyperglycemia and mannitol administration [1,2].

As we can from the formula, the contribution of serum glucose and BUN to plasma osmolality is low, except for two situations: diabetes and renal impairment. But there is a difference between the measured plasma osmolality and effective plasma osmolality (tonicity):

$$corrected\ Posm = measured\ Posm - BUN/2.8$$

BUN is osmolal ineffective; it can freely cross the cell membrane and does not force water to go out of cells. Thus patients with hyponatremia and renal failure have reduced effective plasma osmolality [1,4]. In renal impairment the water intake exceeds the excretion and the result is hypervolemic hyponatremia [1,4].

There are several differences between the clinical conditions with hypervolemic hyponatremia. In acute and chronic renal failure the total body water is high, as is the total body sodium, with hypervolemia as the final result [1,5,6] Hypervolemia appears also in heart failure and cirrhosis with high

levels of total body water and sodium, but one difference between them consists in the level of urinary sodium concentration; it is low (< 10 mmol/L) in heart failure and cirrhosis patients, and high (> 20 mmol/L) in acute and chronic renal failure individuals [1,5]. Another difference between these conditions is the serum level of vasopressin. In congestive heart failure and cirrhosis there is an inadequate suppression of vasopressin release, while in renal failure there is an adequate suppression of vasopressin release [1,7].

In acute renal failure the diminished glomerular filtration rate (GFR) is followed by hyponatremia, because the water intake exceeds the urine output. From the same reason advanced stages of chronic kidney disease (CKD) is accompanied by hyponatremia [1,2].

A particular condition of kidney disease is nephrotic syndrome. Hyponatremia could occur in nephrotic syndrome with hypoalbuminemia (< 2 g/dL) by nonosmotic stimulation of arginine vasopressin (AVP) secretion as the result of intravascular hypovolemia [1,2,4].

Summarizing, depending on effective osmolality and total volume fluid status, hyponatremia can be classified as follows (**Table 1**) [1,8,9]:

Clinical trials

There are only few reports about the prevalence of hyponatremia in the renal failure patients. Wald et al reported a prevalence of hyponatremia in 38.2% in a retrospective study of 53,236 hospitalized patients followed for 7 years [37]. In CKD patients the prevalence of hyponatremia was 3.6% [37].

Furthermore, in end stage renal disease (ESRD) patients, Waikar et al reported a pre-dialysis hyponatremia in 29.3% of cases, correlated with increased mortality [38]. The relationship hyponatremia-mortality was independent of the type of dialysis, heart failure or hypervolemia [38].

Kovesdy observed in a large study on 4.4 million U.S. veterans, that 655.493 patients had CKD, presenting a mean age of 73.9 ± 9.8 years, 87% white and 9% black and a GFR 50.2 ± 14.1 ml/min/1.73 m2 [39]. The prevalence of hyponatremia (< 136 mEq/L) was 13.5% [38]. After an average of 5 years surveillance, 26% developed at least one episode of hyponatremia [39]. Hyponatremia was associated with increased mortality and it was present in all stages of CKD, including in patients with and without heart failure, liver disease, neoplasia and depression [39]. The association hyponatremia-mortality was not affected by different stages of CKD [39].

Therapy management

The rate of hyponatremia correction depends on the severity of hyponatremia, the acute or chronic condition, the mechanism of hyponatremia, the duration, the high risk factors in developing osmotic demyelination syndrome [1,2,40]. Hyponatremia ≤ 120 mmol/L for more than 48 h has a high risk [1,2]. The risk factors for developing osmotic demyelination syndrome are: hyponatremia ≤ 105 mmol/L, hypokalemia, advanced liver disease, malnutrition, alcoholism [1,2]. Minimum correction of serum [Na^+] by 4 – 8 mmol/L/day for high risk patients and 10 – 12 mmol/L/day for normal risk patients is recommended [1,2].

If the hyponatremia is hypervolemic, with edema, the expert panel recommendations are dietary sodium restriction and diuretic therapy [1,2]. The fluid restriction is 500 mL/day below the daily urine volume [1,2]. The probability of failure of fluid restriction is high in case of high urine osmolality, 24 h urine volume less than 1500 mL or increase in serum Na+ level < 2 mmol/L/day in the first 24 – 48 h [1,2].

CKD patients require higher doses of loop diuretics, because of resistance to the effects of diuretics [41]. It is necessary to carefully assess the hydroelectrolytic and acid-base status and treatment replacing of the hypomagnesemia and hypokalemia [41].

Conivaptan and tolvaptan are AVP receptor antagonists approved by FDA in clinical practice for euvolemic and hypervolemic hyponatremia in hospitalized patients [2]. Conivaptan is used intravenous as a 20 mg loading dose in half an hour, followed by a continuous infusion of 20 – 40 mg/day [2]. Tolvaptan is used orally as 15 mg on the first day, with titrated dose to 30 – 60 mg at 24 hour interval if the increase in serum Na+ level is < 5 mmol/L in the previous 24 h [2]. The most important side effect of tolvaptan was liver injury, reported in a study on autosomal dominant polycystic kidney disease [2]. Vaptans don not cause clinically significant side effects if serum creatinine is above 3 mg/dL [2]. A lot of questions regarding the long-term treatment of hyponatremia following patients discharge still remain: the most effective treatments in chronic hyponatremia, the value of chronic water restriction,

the most efficient methods in improving the cognitive function, quality of life or osteoporosis and fractures prevention in these patients [2]. These questions remain to be solved from the next trials.

CONCLUSIONS

Hyponatremia plays an important role in the prognostic and mortality risk of the hospitalized CKD patients. The volemic status, the plasma tonicity, the mechanisms, the severity and the duration of hyponatremia are the keys of management in CKD patients. Therefore, a constant evaluation of clinical status and bioumoral parameters is required in hospitalized CKD patients, and further clinical trials are needed for a better understanding of this pathophysiological mechanism.

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