Thiazide Diuretics Induced Refractory Hyponatremia: Use of Vaptans

International Journal of Cardiology and Cardiovascular Disorder Case Report

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Submitted : 21 May 2021 ; Published : 1 Jul 2021

Abstract

Hyponatremia is a conceivably fatal complication of thiazide diuretics. A loop diuretic, as compared to thiazides, is much less likely to cause symptomatic hyponatremia. We report an unusual case of refractory hyponatremia of 109 meq/L (Normal range (NR): 136-145 meq/L) in a 57-year-old female within two weeks of increasing dose of metolazone, a thiazide-like diuretic. After treatment with intravenous 3% hypertonic saline infusion, fluid restriction and discontinuation of metolazone, and ruling out other possible causes of hyponatremia, the serum sodium levels failed to improve adequately until Tolvaptan was added for a short duration. Our report aims to highlight the life-threatening dilemmas associated with thiazide diuretics and to manage it by careful correction and monitoring of sodium levels with the possible use of vaptans for refractory cases.

Learning Objectives

Thiazide diuretics induced hyponatremia may present as the syndrome of inappropriate antidiuretic hormone, and it is essential to investigate for both if the cause is unclear. Antidiuretic hormone antagonists, like tolvaptan, may be an option to treat refractory hyponatremia due to thiazide diuretics.

Introduction

One of the most common electrolyte abnormalities present in patients, especially on diuretics, is hyponatremia, defined as a serum sodium level less than 135 meq/l. Most reported hyponatremia cases due to diuretics have belonged to the thiazide group [1]. Thiazide diuretics' ability to promote hyponatremia is demonstrated by the interference of urinary dilution due to decreased reabsorption of NaCl in the distal renal tubules. Contrary, loop diuretics do not commonly diminish urinary dilution and are not linked to reducing serum sodium levels [2].

Case Report

A 57-year-old female with a past medical history of coronary artery disease, diabetes mellitus type II, and heart failure with reduced ejection fraction presented to the outpatient department with progressive dizziness, increasing falls, and shortness of breath of two weeks. The patient was found to be severely hyponatremic with a serum sodium level of 109 meq/l. She was immediately shifted to inpatient cardiology, where further history revealed worsening orthopnea, paroxysmal nocturnal dyspnea, and palpitations on rest and exertion.

She had doubled the dose of her thiazide diuretic (metolazone) herself in the last two weeks, which had led to an acute weight loss of 25 lbs. She was transferred to the intensive care unit (ICU) for stringent monitoring. Her electrocardiogram (EKG) revealed QT interval (QT) prolongation with QTc> 560msec. Initial lab investigations showed urine sodium of 27 meq/l, urine creatinine of 32mg/kg/24hr, and a urine osmolality of 226 mosm/kg. In the ICU, the patient was started on 3% hypertonic saline with a goal of correction levels of <8meq/24 hour and furosemide drip for continued diuresis: due to concurrent fluid overload. Overnight her sodium improved to 114 meq/l (Table 1), and the patient was moved out of ICU. Repeat urine osmolality increased from 226 to 292 mOsmol/kg (Table 2). Her furosemide drip and hypertonic saline were discontinued, and she was fluid restricted to 500ml/day. The serum sodium levels failed to improve despite fluid restriction. Because of her significant smoking history and recent falls, she was investigated for the syndrome of inappropriate antidiuretic hormone release (SIADH). Her CT chest and head were negative. Upon nephrology consultation, she was started on tolvaptan, and her sodium levels improved from 119 meq/l to 125 meq/l in a day. Fluid restriction was continued along with tolvaptan which was discontinued after two days. Her sodium levels gradually corrected to her baseline of low 130s meq/l, and she was discharged.

Sodium Lab values	Latest Reference Range: 136 - 145 mEq/L
Day 1	109
Day 2	117
Day 3	122
Day 4	119
Day 5	120
Day 6	125
Day 7	124
Day 8	126
Day 9	131

Table 1: Serum Sodium laboratory values during the course of admission.

Lab Values	Ref. Range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Osmolality, urine	Latest Ref Range: 300 - 900 mOsmol/kg	226	292	288	255	259	146	197
Sodium, urine	Latest Ref Range: 40 to 220 mEq per day	27	N/A	47	31	21	<20	26

Table 2: Urine osmolality and sodium trends during the course of hospital admission.

Discussion

Hyponatremia displays an array of prognostic implications in various conditions, with an estimated prevalence of 1.72% in the general population (United States) having a significant potential for morbidity and mortality [3]. The severity of hyponatremia is categorized into mild (130-134 meq/l), moderate (125-129 meq/l), and severe (<125 meq/l) per joint European guidelines. Three basic mechanisms underly its etiology; Mechanistic descriptions include hypertonic (dilutional), isotonic (pseudo hyponatremia), or hypotonic (which may be hypervolemic, euvolemic, or hypovolemic hyponatremia) [3, 4]. Hyponatremia can also be classified according to the duration of time since onset as acute when less than 48 hours and Chronic if more than 48. Patients with acute hyponatremia develop neurologic symptoms resulting from cerebral edema, including seizures, impaired mental status, coma, or death [5]. Conditions associated with chronic hyponatremia are more frequent and severe in elderly patients [6]. Our patient with severe chronic hyponatremia appeared to be euvolemic clinically. Most Commonly, Euvolemic hyponatremia includes glucocorticoid deficiency, hypothyroidism, primary polydipsia, beer potomania, and exercise. However, none of these were consistent with our case's history or laboratory findings except Syndrome of inappropriate antidiuretic hormone secretion (SIADH) or an adverse reaction to a diuretic as probable causes [3, 4]. Thiazide Induced Hyponatremia (TIH) holds a strong resemblance with SIADH [7, 8]. SIADH diagnostic criteria dictate observation of elevated urinary osmolality and urinary sodium and zero utilization of diuretic use for at least seven days, is a requisite [3], thus leading to TIH as the most plausible cause in our case. However, the patient did continue to display low serum sodium levels with increased urine osmolality despite sodium restriction even one week after stopping thiazide diuretic but responded well to tolvaptan. Hyponatremia is a potentially fatal complication of diuretic therapy with low body mass, older age, female gender, an increased dose of thiazides, co-morbidities, and polypharmacy [7, 8]. Intriguingly the time of onset TIH is unpredictable, ranging from weeks to years [8]. The clinical manifestations of TIH can develop acutely or progressively, being analogous to those due to other causes of hyponatremia, ranging from mild to severe and from asymptomatic to symptomatic [1, 3]. Thiazide diuretics being an effective and inexpensive prescription, are most widely used for the treatment of hypertension [7], which raises the concern of cautious-approach, close monitoring, and follow-up for electrolyte disturbances. Patients with severe symptomatic hyponatremia can develop life-threatening or lethal complications from cerebral edema. Permanent neurologic disability from osmotic demyelination syndrome (ODS) is another complication if electrolyte disturbance is treated with haste [4-8]. The treatment should be individualized, and the cause, acuity, and associated symptoms must be considered. The majority of the authors acknowledge the halting of medication as the initial approach for TIH [3-9]. However, there appears to be little consensus on fluid administration. Hwang and Kim [9] recommend discontinuing thiazides, regular diet (usually supplemented with K+), restricting water, administration of furosemide, and either isotonic saline or, if the hyponatremia is severe or symptomatic, the hypertonic saline infusion is required. Liamis, et al. recommends administering hypertonic saline in acute symptomatic hyponatremia, while in chronic euvolemic oligosymptomatic hyponatremia, water restriction may suffice, and in chronic hypovolemia, normal saline should be administrated. Simultaneously, discontinuation of diuretic therapy remains a standard edge to all the approaches [8].

When treated with fluid restriction, hyponatremia patients show poor compliance over the long term [10]. Vasopressin receptor antagonists (Vaptans) have been used in numerous clinical scenarios, but success has been limited. Vasopressin receptor antagonists produce their action on vasopressin type 2 (V2R) receptors in the collecting duct, decrease the action of Antidiuretic hormone and thus enhance solute free water excretion [10]. Vaptans may be used as an additional option as a short-term solution. According to Girish, et al., vaptans' efficacy for the management of hyponatremia is well accepted for shorter durations. However, it has not been established whether they effectively improve the mortality and morbidity in patients presenting with acute or chronic hyponatremia, either due to diuretic use or heart failure [10]. Hyponatremia due to TIH remains a challenge due to the significant overlap of symptoms with SIADH. Thiazides interfere with renal water excretion; they impair the normal osmoregulatory response [7]. Thus, in patients with hyponatremia, urine osmolality is inappropriately high relative to the osmolality of plasma and often exceeds it, mimicking SIADH [9]. Moreover, there are no randomized trials to guide the treatment; instead, therapeutic decisions rest on observational studies. Our case is an essential contributor to the body of literature as it highlights the dangerous complications and management of TIH-induced hyponatremia. Adding vaptans for a shorter duration in cases where an increase in serum sodium serum concentration is refractory to fluid restriction is an option that needs more data.

Conclusions

Metolazone is commonly used as an adjunct to loop diuretics for fluid overload in heart failure patients. Its association with severe hyponatremia and presentation similar to SIADH has been rarely reported in the literature. We highlight the use of vaptans for refractory cases of TIH induce hyponatremia; Further comparative data and randomized control trials would be helpful in the future to shed more light on the use of vaptans for diuretic-induced hyponatremia.

Acknowledgements

We thank the patient for providing authorization for medical record use.

Author contributions

HA Conceptualization, Writing-Review & Editing, Supervision, Project Administration

WA: Investigation, Resources, Writing-Original Draft, Visualization

SS: Investigation, Resources, Writing-Original Draft

Competing interests

The Authors declare that there is no conflict of interest.

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