CASE REPORTS

Vasopressin-induced hyponatremia in a patient with pulmonary hypertension and right heart failure treated for septic shock

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ABSTRACT

We report a case of a 55-year-old woman who developed hyponatremia after the initiation of exogenous vasopressin to treat vasodilatory shock. Discontinuation of exogenous vasopressin therapy, without any other changes in medical therapy or the patient's condition, led to a rapid correction in the serum sodium level along with a marked increase in urine output. Increased free water retention due to exogenous vasopressin administration may have contributed to hyponatremia in this patient. This case illustrates the potential for vasopressin to have potent and unintended renal and electrolyte effects in patients treated for vasodilatory shock.

Key Words: Hyponatremia, Septic shock, Pulmonary hypertension, Heart failure

1. INTRODUCTION

Exogenous vasopressin is used in vasodilatory shock to support a falling systemic vascular resistance (SVR) and mean arterial pressure (MAP), with its effect mediated via repletion of reduced vasopressin stores in circulation.[1,2] Conversely, patients with heart failure (HF) exhibit elevated levels of endogenous vasopressin, which contributes to vasoconstriction and free water retention.[3] The development of hyponatremia from exogenous vasopressin administration is rarely reported.[1,4] Here we discuss a case of vasopressin-induced hyponatremia in a patient with pulmonary hypertension (PH) and right ventricular (RV) failure. We also explore the pathophysiology of vasopressin and its receptors in vasodilatory shock and the potential mediation of its effects in HF.

2. CASE REPORT

A 55-year-old woman with chronic thromboembolic pulmonary hypertension and persistent PH with RV failure 13-days status-post pulmonary thromboendarterectomy was transferred to the intensive care unit for hypoxic respiratory failure and septic shock. The patient was hypotensive with a blood pressure of 90/52 mmHg, febrile to 101.2 F, tachypneic, and tachycardic. Physical examination revealed respiratory distress, elevated jugular venous pressure of 12 cm and an RV heave. Laboratory studies were notable for leukocytosis and a mixed venous oxygen saturation of 51% (hemoglobin 10 mg/dl; normal range of 12-15.5 mg/dl). A transthoracic echocardiogram demonstrated a normal left ventricular ejection fraction with a markedly reduced RV systolic function, paradoxical septal motion, and septal flat-

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tening suggestive of persistent PH and RV failure despite recent thromboendarterectomy.

The patient was intubated and started on vancomycin 1 g q12H and piperacillin/tazobactam 1.5 g q8H for presumed sepsis. She was continued on sildenafil 40 mg q8H and started on inhaled nitric oxide 20 PPM for persistent PH. The patient also required vasopressin which was quickly up-titrated to a maximum dose of 0.04 units/min as a result of persistent hypotension and low SVR. Given that her MAP remained around 55 mmHg, norepinephrine was added and titrated up to a dose of 10 mcg/min to maintain a MAP greater than 60 mmHg. Repeat hemodynamics on vasopressor therapy revealed a central venous saturation of 58%, a cardiac output of 5.5 L/min, and an SVR of 800 dynes consistent with vasodilatory shock. In the next 72 hours, the patient became oliguric and hyponatremic (see Figure 1), with serum sodium levels decreasing from 141 to 126 meq/L (normal 135-145 meq/L). Although her urinary sodium was not checked, serum osmolality was 263 mosm/kg (normal 275-295 mosm/kg) which was suggestive of dilutional hyponatremia. A concomitant rise in her jugular venous pressure suggested associated fluid overload. The fasting serum glucose levels of 90-107 mg/dl (normal 70-100 mg/dl) excluded pseudo-hyponatremia as a potential cause. The Naranjo algorithm, which evaluates the odds of an adverse drug reaction being the cause of a given clinical presentation, yielded a score of 7 – consistent with a probable drug reaction.[5] Review of the patient's medications revealed that vasopressin was likely the culprit and it was discontinued.

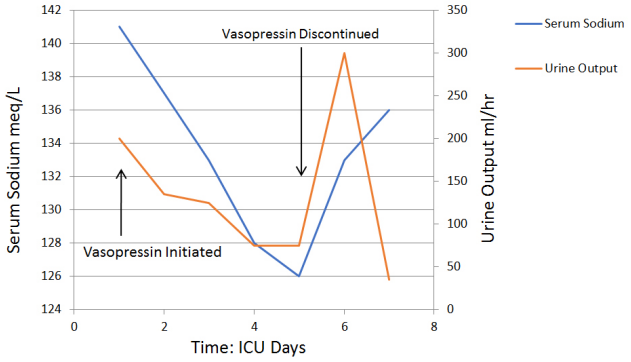

Figure 1. Graph of serum sodium levels and urine output versus time

Immediately after stopping vasopressin, and without any significant changes in her condition or additional hemodynamic support, her urine output increased from 75 to 300 cc/hr for the next 15 hours. To prevent rapid overcorrection of the serum sodium, 5% dextrose in water was initiated. Over the next 24 hours, the serum sodium levels increased to 136 meq/L (see Figure 1) and she was able to be weaned off vasopressor support. Following clinical stabilization and marked improvement of her PH, the patient was discharged home and continues to follow on an outpatient basis.

3. Discussion

Vasopressin acts on three principal G protein-coupled receptor types.[6] Vasopressin 1 (V1R) receptors are found in vascular smooth muscle where their activation leads to potent vasoconstriction.[6] Vasopressin 2 (V2R) receptors mediate the antidiuretic effect, which results in free water absorption by increasing the osmotic permeability of the renal collecting duct.[6,7] Finally, vasopressin 3 receptors are involved in the release of adrenocorticotropic hormone from the pituitary.[6,8]

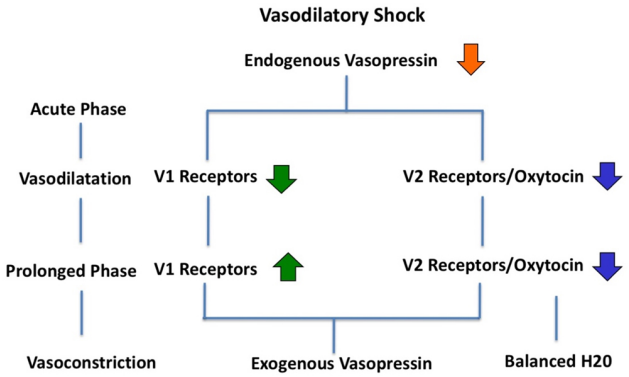

Figure 2. Vasopressin level and receptor expression in vasodilatory shock

In the initial stages of vasodilatory shock, there is a brief surge in the endogenous vasopressin level;[9] however, this quickly leads to vasopressin depletion and resultant vasodilatation (see Figure 2).[9,10] Research in a rat model has demonstrated that V1R expression decreases acutely in the liver, lung, kidney, and heart in the setting of endotoxemia thereby reducing the body's ability to maintain vascular tone.[11] However, prolonged duration of vasodilatory shock results in vasopressin hypersensitivity – a process which is thought to be mediated by either increased V1R binding availability due to decreased levels of circulating endogenous vasopressin, an increase in receptor expression, or increased binding affinity of V1R.[2] V2R expression has been shown to be decreased in vasodilatory shock (see Figure 2).[12,13] Vasopressin also acts on oxytocin receptors which stimulate the release of atrial natriuretic peptide and can result in increased urinary sodium excretion and naturesis; however, oxytocin receptor expression is also decreased in vasodilatory shock.[2] At low doses, vasopressin activates purinergic receptors which mediate vasodilation - an effect

that is counteracted with high vasopressin doses at which V1R stimulation results in vasoconstriction.[14] This means that exogenous vasopressin can be used to increase blood pressure is sepsis without causing noticeable water retention.

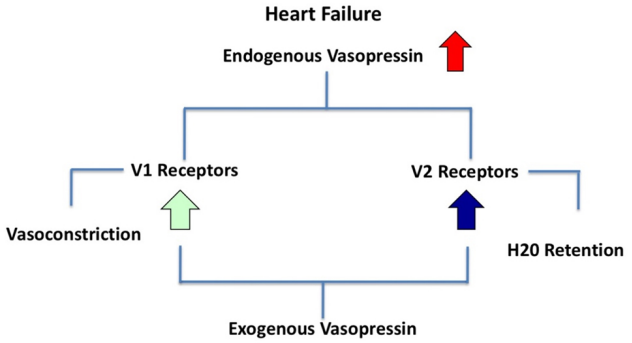

Figure 3. Vasopressin level and receptor expression in heart failure

In contrast, endogenous vasopressin levels are elevated in the setting of clinical HF, including RV failure from pulmonary arterial hypertension (PAH) (see Figure 3).[15] Studies have shown that neurohormonal axis activation occurs in right-sided HF states to a degree similar to HF from left-sided cardiac dysfunction.[16] This likely explains the association between serum hyponatremia, RV dysfunction and poor prognosis in patients with PAH.[17] In HF, vasopressin accounts for vasoconstriction and potentiates the effects of the renin-angiotensin system and norepinephrine thereby leading to pathologic cardiac remodeling.[18,19] Vasopressin also regulates water homeostasis, which contributes to hypervolemia in HF.[20] Recent findings from a post-mortem study of failing human hearts indicated that V1R expression is increased.[21] A study of cardiomyopathic hamsters demonstrated that V2R expression is increased in the kidneys in HF.[22] Consequently, increased V1R and V2R expression in HF may explain the pathologic nature of vasopressin (see Figure 3). Future studies are needed to confirm whether HF predisposes patients treated for vasodilatory shock to the unintended renal and electrolyte effects of exogenous vasopressin.

Vasopressin induced hyponatremia is reported infrequently in the literature. A recent retrospective review by Marr et al. illustrated that patients who received vasopressin infusion for management of subarachanoid hemorrhage were at an increased risk for developing hyponatremia (OR 3.58, 95% CI, 1.02-12.5).[23] In the randomized, double-blind Vasopressin and Septic Shock (VASST) trial comparing vasopressin infusion to norepinephrine infusion, only one patient developed hyponatremia (sodium < 130 meq/L) out of the 396 patients treated with vasopressin.[1] Finally, Salazar et al. reported 2 cases of hyponatremia associated with vasopressin infusion to treat vasodilatory shock. The mechanism was attributed to the anti-diuretic effect of vasopressin, which is also implicated in our case.[4]

4. Conclusion

While exogenous vasopressin-induced hyponatremia is seemingly rare, the potential physiologic modulation of vasopressin in the setting of HF may make the unintended renal effects of vasopressin a more dramatic and common occurrence. This case illustrates the potential for rapid and reversible hyponatremia due to exogenous vasopressin administration in a patient with HF treated for vasodilatory shock. In addition, the case highlights the importance of careful electrolyte monitoring in this setting.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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