Fanconi and Inappropriate Secretion of Antidiuretic Hormone Syndromes Secondary to Venlafaxine Therapy

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Venlafaxine, a 2-phenyl-2 (1-hydroxycycloalkyl) ethylamine derivative, is an inhibitor of both serotonin and norepinephrine re-uptake and was termed a 'dual uptake inhibitor' [1]. We report on a venlafaxine-treated patient who developed Fanconi's syndrome (FS) and hyponatremia secondary to inappropriate antidiuretic hormone secretion syndrome (SIADH).

Case Report

An 82-year-old woman with chronic alcohol abuse, hyponatremia (128 mmol/l), and essential hypertension treated by atenolol 50 mg daily was admitted to hospital for depression. On examination, she presented with anxiety disorder and mental confusion. She had no fever and blood pressure and heart rate were 120/80 mm Hg and 85 beats/min, respectively. Neither dehydration nor edema was noted. Despite incoherent speaking, no localizing neurological signs of meningitis were observed. Her serum sodium level was 128 mmol/l, potassium 4.4 mmol/l, chloride 94 mmol/l, total carbon dioxide 28 mmol/l, blood urea 5.2 mmol/l, serum creatinine 82 μ mol/l, serum uric acid 388 μ mol/l, calcium 2.4 mmol/l, phosphate 1.2 mmol/l, and glucose level 5.2 mmol/l, and anion gap 14 mmol. Urinalysis revealed a ++ glycosuria, ++ proteinuria, and urine pH at 5. Chest X-ray, cerebral computer angiotomography scan were normal as for adrenal, thyroid tests, and liver function. Urine osmolality, sodium,

potassium, and urea were 370 mosm/kg, 60 mmol/l, 20 mmol/l, and 210 mmol/l, respectively.

The patient was treated with venlafaxine 50 mg, twice daily. Four days after the start of treatment, electrolytes were sodium 111 mmol/l, potassium 3.7 mmol/l, chloride 85 mmol/l, total carbon dioxide 19 mmol/l, blood urea 2.8 mmol/l, serum creatinine 37 μ mol/l, serum uric acid 58 μ mol/l, serum phosphate 0.49 mmol/l, serum glucose 4.5 mmol/l, and anion gap 14 mmol with urine pH at 6.5 and glycosuria in spite of normal glycemia. Serum ADH level was 2.5 IU/ml (normal range 0.5–1.5) and plasma and urine osmolality were 238 and 390 mosm/kg, respectively. Acquired Fanconi's syndrome and SIADH induced by venlafaxine were diagnosed. The patient required hydric restriction, isotonic saline solution infusion (500 ml/day) and venlafaxine was withdrawn. After 2 days, electrolyte levels improved and were total carbon dioxide 26 mmol/l, serum uric acid 100 μ mol/l, and serum phosphate 0.99 mmol/l. One week after venlafaxine was withdrawn, serum sodium was 130 mmol/l. The patient's condition gradually improved and she was discharged after 2 weeks having fully recovered her normal baseline mental status.

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Table 1. Reports of venlafaxine-induced hyponatremia

Author	Patient age/sex	Venlafaxine use		Hyponatremia		
		indication	dosage mg/day	time between venlafaxine introduction and diagnosis	time between venlafaxine withdrawal and trouble correction	mechanism
Gupta and Saravay [3], 1997	76/F	depression and associated anxiety	50 then 75	1 week	1 week	SIADH
Meynaar et al. [4], 1997	65/M	presumed depression	75	1 week	2 weeks	SIADH
Ranieri et al. [5], 1997	79/F	depression	–	–	–	ROS
Masood et al. [2], 1998	92/F	depression	75	–	few weeks	SIADH
Our patient	82/F	depression and associated anxiety	50 then 100	2 days	4 days	SIADH

SIADH = Syndrome of inappropriate antidiuretic hormone secretion; ROS = reset osmostat syndrome.

Discussion

Venlafaxine is a serotonin re-uptake inhibitor that inhibits not only serotonin but also norepinephrine re-uptake. Clinically significant hyponatremia has been reported as a side effect of its utilisation [2] by SIADH [3, 4], and reset osmostat syndrome [5].

Our patient had a history of chronic alcohol abuse and essential hypertension treated with atenolol. It is well known that hyponatremia is commonly reported in chronic alcoholic patients (17.3%) [6] and has been attributed to hypovolemia, pseudohyponatremia with alcohol-induced severe hypertriglyceridemia, 'beer potomania syndrome' and reset osmostat syndrome (ROS) or cerebral salt wasting syndrome. On admission, our patient did not present any clinical symptoms of extracellular dehydration or hyperhydration. Furthermore, serum triglyceride, glucose, protide levels were normal at 1 mmol/l, 5 mmol/l, and 70 g/l, respectively.

The syndrome of 'beer potomania' hyponatremia is due to a large consumption of beer together with a minimal intake of ordinary food such as in our patient. However, beer drinkers typically produce less than 250 mosm of solutes a day, and urine osmolality in our patient at admission was higher than 350 mosm. We thus believe that initial hyponatremia in our patient was due to a reset osmostat syndrome variant of SIADH because of a chronic asymptomatic hyponatremia of moderate severity (125–130 mmol/l) and that it was not corrected with adequate sodium chloride loading (130 mmol/l). The typical features of SIADH are hyponatremia, low serum osmolality, high urine osmolality and urine sodium excre-

tion which is inappropriately high with regard to serum sodium concentration.

The risk of SIADH secondary to antidepressant drugs seems to be higher in the first few weeks of treatment [7]. Several cases of venlafaxine-induced hyponatremia have been reported in the literature (table 1). The development of hyponatremia appears within a week after the start of venlafaxine therapy. Our patient developed acute hyponatremia 2 days later. Return to baseline serum sodium level after treatment is withdrawn requires a few days with a gradually mental status improvement such as in our patient. In Australia, the Adverse Drug Reactions Advisory Committee has received 234 reports of suspected adverse reactions in association with this drug [8]. Fifteen reports of hyponatremia were detected between 3 and 20 days (median 9) after initiation of therapy, with minimum values of serum sodium concentrations ranging from 116 to 130 mmol/l (median 124). Associated symptoms including confusion (3 cases), syncope, nausea, fatigue, hallucination, agitation, convulsions, delirium, and ataxia were reported in 7 cases. SIADH was suspected in 7 reports but was confirmed in only 1. This adverse effect seems to be dose dependent: asymptomatic hyponatremia with a 50-mg daily dosage and neurologic and psychiatric symptoms at a 75 mg or more daily dosage [3]. Medication management includes venlafaxine withdrawal, fluid restriction, and infusion of normal saline. In some cases, the use of furosemide, along with careful monitoring of her intake and output has been recommended.

Venlafaxine has been shown to induce hyponatremia (table 1) particularly in patients whose sodium reserve has been depleted because of dietary restriction or diuretic

use. However, its effect on proximal tubular is unknown, and the real mechanism of venlafaxine-induced Fanconi's syndrome remains unclear. The acute combination of normal anion gap metabolic acidosis with alkaline urine pH (of renal tubular origin), glycosuria in spite of normal serum glucose, low serum uric acid and phosphate concentrations and hypokaliemia are highly suggestive of acquired Fanconi's syndrome.

All abnormalities in our patient were transient, with recovery occurring 4 days after venlafaxine withdrawal.

Physicians should keep in mind the possible occurrence of or be alerted to the possibility of SIADH and Fanconi's syndromes induced by venlafaxine. Therefore, tubular function, electrolytes and acid-base statements should be monitored in patients treated with venlafaxine.

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