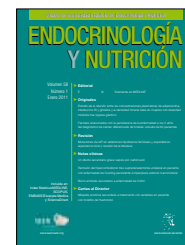




# ENDOCRINOLOGÍA Y NUTRICIÓN

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## LETTER TO THE EDITOR

### Paroxetine, hypothyroidism and, despite everything, inadequate antidiuretic hormone secretion

Paroxetina, hipotiroidismo, y a pesar de todo, secreción inadecuada de hormona antidiurética

*To the Editor:*

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) indicated for major depression, obsessive-compulsive disorder, social anxiety and phobia disorder, generalized anxiety disorder, and panic disorder. Known adverse reactions to paroxetine include inappropriate antidiuretic hormone secretion syndrome (SIADH)<sup>1</sup>, consisting of hyponatremia, plasma hypo-osmolality, inappropriately high urinary osmolality, and urinary sodium levels usually higher than 40 mmol/L. From the classical concept of SIADH it is inferred that, as this is an exclusion diagnosis, the presence of certain conditions, such as adrenal insufficiency or hypothyroidism, would invalidate a diagnosis of SIADH, even though these conditions are considered to cause both a physiological elevation of arginine-vasopressin and SIADH<sup>2</sup>. We report the case of a female patient who experienced significant hyponatremia a few days after starting treatment with paroxetine and who was diagnosed with SIADH and primary hypothyroidism.

This 81-year-old female patient reported depression during the previous months, and had therefore been taking paroxetine 10 mg/day for the past 12 days. One month before admission, normal sodium levels (141 mmol/L) and high total cholesterol levels (261 mg/dL) had been found. No thyroid function values were available. The patient attended the clinic for fatigue, drowsiness, and an impaired general state following the start of paroxetine treatment. Physical examination revealed bradypsychia, myxedematous face, and generalized hyporeflexia. There was no edema, nor were there signs of dehydration. Complete blood count showed anemia (hemoglobin, 11.3 g/dL) with normal mean corpuscular volume and erythrocyte sedimentation rate of 26 mm. Chemistry results were normal except for total cholesterol, 228 mg/dL; uric acid, 1.5 mg/dL (normal range [NR], 2.4–5.7); plasma sodium, 114 mmol/L; plasma osmolality, 238 mOsm/kg; urinary sodium, 89 mmol/L; and

urinary osmolality, 395 mOsm/kg (NR 300–1,400 mOsm/kg). Basal cortisol levels were normal, and thyroid function tests demonstrated primary hypothyroidism (TSH, 52.67  $\mu$ U/mL [NR, 0.25–5]; free thyroxine, 0.88 pg/mL [NR, 7–18]; and free triiodothyronine, 0.60 pg/mL [NR, 2–4.25]).

Paroxetine-induced SIADH was initially suspected. The drug was therefore discontinued, isotonic saline was administered, and water intake was restricted. At 72 hours, patient was symptom-free and with sodium levels of 134 mmol/L. One month later, after starting levothyroxine replacement therapy, sodium levels had normalized (140 mmol/L), but hypothyroidism persisted (TSH 21.67  $\mu$ U/mL, free thyroxine 7 pg/mL, and free triiodothyronine 1.89 pg/mL).

SIADH is a well known and potentially serious adverse reaction to paroxetine<sup>3</sup>. Wilkinson et al<sup>4</sup> found an incidence of frank hyponatremia of 3.5 cases/1,000 patients/year. Mild hyponatremia may however occur in up to 25% of patients treated with SSRIs<sup>5</sup>. Mean time to hyponatremia is approximately 13 days, and hyponatremia occurs in more than 80% of patients within one month of treatment<sup>6</sup>. SIADH appears to be caused by the role of serotonin in arginine-vasopressin synthesis<sup>7</sup>. Factors promoting the development of SIADH by SSRIs include advanced age, concomitant treatment with diuretics, and low weight<sup>2,8</sup>. Paroxetine prescribing information therefore advises precaution regarding patients at risk of hyponatremia, with concomitant medication or with liver cirrhosis<sup>1</sup>. Such recommendations could also be applicable to patients with hypothyroidism. Hypothyroidism is frequently associated with hyponatremia, particularly in cases of myxedematous coma<sup>9</sup>. A decreased renal capacity to excrete water (due to decreased renal flow and glomerular filtration rate and to abnormalities in proximal and distal nephron segments) and increased vasopressin levels, both of which are found in a significant number of these patients, are factors that could explain hyponatremia.

Our patient very likely had long-standing hypothyroidism, and her sodium levels were normal. However, SIADH was directly triggered by the use of paroxetine, despite the fact that it was promoted by the underlying thyroid disease. Based on this, and on the normalization of sodium levels after paroxetine discontinuation (despite the persistence of hypothyroidism), we believe that paroxetine-induced SIADH and primary hypothyroidism coexisted in our patient.

Finally, we find particularly worrying the comment by Clayton et al<sup>10</sup> that they did not find any adequately studied cases of suspected SIADH. The need for adequate identification and management of SIADH should therefore be emphasized.

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