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Syndrome of inappropriate secretion of antidiuretic hormone associated with paroxetine

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Abstract A 71-year old man with failed back syndrome was admitted to hospital with oliguria that had occurred 4 days after his dose of paroxetine had been increased to 40 mg·day^{-1}. Laboratory data on admission revealed hyponatremia (124 mmol·l^{-1}), low serum osmolarity (267 mOsm·l^{-1}) with a normal level of serum antidiuretic hormone (1.7 pg·ml^{-1}), and concentrated urine (430 mOsm·l^{-1}). He was diagnosed as having syndrome of inappropriate secretion of antidiuretic hormone, associated with paroxetine; this drug was discontinued immediately after admission. The hyponatremia was treated with saline infusion, water restriction, and furosemide; serum sodium level returned to normal on hospital day 5. Paroxetine is being increasingly used for depression and chronic pain management because of its favorable side-effect profile; however, we should be alert to hyponatremia in patients on paroxetine by carrying out periodic monitoring of serum electrolytes, especially in elderly patients.

Key words Paroxetine · Hyponatremia · Syndrome of inappropriate secretion of antidiuretic hormone

Introduction

Antidepressants are now widely used as adjuvant analgesics for the treatment of chronic pain. In particular, tricyclic antidepressants (TCAs) have been used for various types of intractable pain; convincing evidence for the in use in the treatment of diabetic neuropathy and postherpetic neuralgia has been well established [1]. However, TCAs have potent anticholinergic action, causing uncomfortable side effects, including dry mouth, constipation, and urinary retention [1]. Recently, selective serotonin reuptake inhibitors (SSRIs) have been preferably prescribed for depression in Japan. Paroxetine is the most potent inhibitor of serotonin uptake among the SSRIs, and has been reported to be beneficial for chronic pain management [2,3]. Paroxetine could be increasingly used for various types of chronic pain because of its favorable side-effect profile and safety; however, hyponatremia, or syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with paroxetine, has been reported [4–12]. This complication is relatively rare, but some patients have manifested severe neurological symptoms [6,8,11,12]. We herein report a case of SIADH associated with paroxetine in order to recommend the periodic monitoring of serum electrolytes in patients on paroxetine to prevent life-threatening hyponatremia.

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Case report

A 71-year-old man with a history of lumbar disk hernia and lumbar spinal canal stenosis was admitted to the orthopedic department at our hospital complaining of oliguria. He had undergone an operation on the lumbar spine 2 years previously; however, his lower back pain and bilateral leg pain had not yet been alleviated. He had also complained of various symptoms, including headache, general weariness, and insomnia. The orthopedist diagnosed failed back syndrome with a depressive state. Paroxetine 10 mg·day^{-1} had been prescribed 10 months before the present admission and the dose had been gradually increased. The oliguria developed 4 days after the daily dose of paroxetine was increased to 40 mg. Other medications he was taking at the time of admission included etodolac 400 mg·day^{-1}, eperisone hydrochloride 100 mg·day^{-1}, and limaprost alfadex 15 μg·day^{-1}. Examination at the urology department showed no organic stenosis causing the oliguria. Laboratory results on admission revealed hyponatremia (124 mmol·l^{-1}) and low serum osmolarity (267 mOsm·l^{-1})

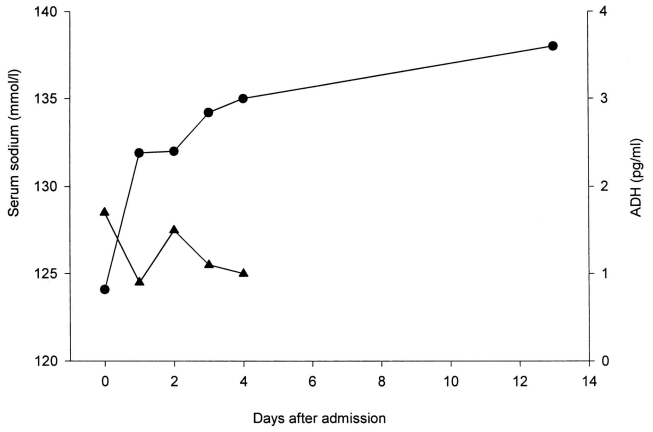

Fig. 1. Serum sodium and serum antidiuretic hormone (*ADH*) levels in the present patient. *Closed circles* and *closed triangles* represent serum sodium and ADH levels, respectively

with a normal level of serum antidiuretic hormone (ADH, 1.7 pg·ml^{-1}; normal range, 0.3–3.5 pg·ml^{-1}; Fig. 1) and concentrated urine (430 mOsm·l^{-1}). Other laboratory data on liver, kidney, and thyroid function were within the normal ranges. He was admitted to our department of anesthesia for treatment of the hyponatremia. Our initial diagnosis was paroxetine-induced SIADH, and therefore paroxetine was discontinued on admission. We administered furosemide 20 mg intravenously and initiated saline infusion with oral fluid restriction (500 ml·day^{-1}) for 3 days. Urine volume had increased to 2500 ml·day^{-1} on the day after admission and serum sodium level returned to normal on hospital day 5. Oliguria was not observed again, even after termination of the above therapy. Serum ADH levels were within the normal range during the first 5 days (Fig. 1). The patient was discharged from our hospital on day 14, with normal serum sodium level and urination.

Discussion

SIADH is a condition produced by the sustained release of ADH in the face of hypotonic extracellular fluid, resulting in hyponatremia. The hallmark of SIADH is concentrated urine in the face of hypotonic plasma. In the present patient, concentrated urine and oliguria were observed despite low plasma osmolarity. Although his plasma ADH level did not increase, it was not appropriately suppressed by the osmotic influence that was similar to findings in a previous report [10].

Although hyponatremia and SIADH caused by SSRIs are being increasingly reported, the early symptoms are likely to be overlooked, because the incidence of hyponatremia induced by paroxetine is not so high ($3.5 \cdot 1000^{-1} \cdot \text{year}^{-1}$) [9]. Up to 1995, 736 cases of hyponatremia and SIADH associated with SSRI use had been reported worldwide; paroxetine was involved in 12.4% of the cases [4]. Compared with TCAs, SSIRs are more likely to cause SIADH [9]. The large majority of the patients who developed hyponatremia induced by SSRIs were older patients [4,9]. Especially, low body weight is a particular risk factor [9]. Furthermore, concomitant medication with diuretics and neuroleptics is another predisposing factor for the hyponatremia induced by SSRIs [12]. Severe hyponatremia is a life-threatening condition. It can cause several neurological deficits, including coma, seizure, and delirium. Thus, we should be alert for the early symptoms of hyponatremia in these patients.

Previous reports showed that hyponatremia associated with SSRIs usually developed soon after the start of the drug therapy [4]. In the most rapidly developed case, serum sodium level dropped to 110 mmol·l^{-1} 2 days after medication with paroxetine 20 mg·day^{-1} [6]. It has been reported that the median time to the onset of SIADH was 13.5 days, with 79% of the cases occurring within 3 weeks after the initiation of fluoxetine or paroxetine therapy [9]. Thus, laboratory examination at 2–4 weeks after the initiation of therapy is recommended to detect the majority of cases [4,9]. In the present patient, hyponatremia was noted 10 months after the start of paroxetine administration. The symptoms developed 4 days after the dose of paroxetine was increased to 40 mg/day. Thus, the present case suggests that we should be aware of the risk of SIADH after the dose of paroxetine is increased, even though no symptoms developed with a lower dose. Routine monitoring of serum sodium should be a requirement after the dose is increased.

Although we administered furosemide to the present patient, it is not always necessary to use this drug for treatment if the symptoms are not severe. Discontinuation of the SSRI and ensuring that extracellular volume is normal are the major aspects of treatment [5]. In almost all patients, the hyponatremia was reversed after the withdrawal of the SSRI [4]. Probably, water restriction and stopping the medication would have been adequate treatment in the present patient Intravenous hypertonic saline infusion or furosemide administration was performed in patients with life-threatening hyponatremia with severe neurological symptoms [11,12]; however, we should be careful to guard against the development of central pontine myelinolysis, which can be caused by the rapid correction of serum sodium levels.

In conclusion, we presented a case of SIADH induced by paroxetine. Periodic examination of serum electrolytes is needed during paroxetine administration, especially in older patients.

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