Abstract

We present a 79-year-old woman with severe hyponatremia secondary to resumption of treatment with paroxetine, a selective serotonin-reuptake inhibitor antidepressant. Confusion and fatigue followed re-initiation of paroxetine after a 3-month hiatus. Hyponatremia, serum hypoosmolality, and urine hyperosmolality strongly suggested the syndrome of inappropriate secretion of antidiuretic hormone. Hyponatremia was quickly resolved after discontinuation of paroxetine and initiation of intravenous normal saline infusion together with oral fluid restriction. This case underscores the importance of monitoring serum sodium in elderly patients taking paroxetine, whether this represents a new prescription or reintroduction of the drug.

Key words: syndrome of inappropriate secretion of antidiuretic hormone (SIADH), selective serotonin-reuptake inhibitor (SSRI), paroxetine

Introduction

Since the late 1980s a number of selective serotonin-reuptake inhibitor (SSRI) antidepressants have been introduced in Western countries (1–8). These drugs have been used widely for depressed patients because of fewer side effects and relative safety compared with tricyclic agents in potential overdose situations. Unlike such older antidepressants, the new drugs involve little risk of postural hypotension, anticholinergic effects, or cardiotoxicity. Recently, however, hyponatremia and/or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) have become recognized as a side effect of all SSRIs. Few reports of these adverse effects have originated from Japan, where SSRIs (fluvoxamine maleate and paroxetine) have been available for clinical use only since 1999 (9, 10). Here, we describe a patient who developed severe hyponatremia most likely related to SIADH shortly after resumption of paroxetine treatment, although symptomatic hyponatremia had not occurred during the initial treatment with the drug.

Case Report

A 79-year-old woman was admitted to our hospital because of confusion and fatigue. Her previous medical history included hypertension, ischemic heart disease, cerebral infarction, and paroxysmal atrial fibrillation. For 1.5 years she had been treated successfully with paroxetine, initiated at 10 mg/day, for post-stroke depression. A review of past laboratory findings disclosed a serum sodium concentration of 129 mEq/l (normal, 135 to 147) 1 week after initiation of paroxetine. However, the patient’s condition did not deteriorate at the time, and 1 month later the serum sodium concentration had normalized spontaneously to 138 mEq/l. Increasing the dose of paroxetine to 20 mg/day was associated with further clinical improvement. Although the patient had stopped using the drug 3 months before admission, she noted dizziness after stopping paroxetine. Four weeks before admission, laboratory examinations had shown no abnormalities: serum sodium, 141 mEq/l; potassium, 3.3 mEq/l (normal, 3.3 to 5.0); chloride, 103 mEq/l (normal, 98 to 108); blood urea nitrogen, 19.4 mg/dl (normal, 9 to 23); creatinine, 0.7 mg/dl (normal, 0.5 to 1.0); and uric acid, 5.9 mg/dl (normal, 2.6 to 6.0). Three days prior to admission she resumed paroxetine treatment at 20 mg/day. Concomitant medications included nifedipine, losartan, disopyramide, isosorbide dinirate, aspirin, and warfarin.

On admission, blood pressure was 180/88 mmHg; heart rate was 85/min with a regular rhythm. The patient was con-
Paroxetine-induced Hyponatremia

Figure 1. Therapeutic measures and changes in serum sodium concentration over the patient’s course.

fused, with intermittently incoherent speech, but was responsive to verbal stimuli and oriented to time and place. Other physical and neurologic examination disclosed no abnormalities except for mild residual right hemiparesis from cerebral infarction 2 years previously. Skin turgor was normal, and no peripheral edema was detectable. Laboratory results included serum sodium of 112 mEq/l; potassium, 2.8 mEq/l; chloride, 79 mEq/l; blood urea nitrogen, 15.2 mg/dl; creatinine, 0.4 mg/dl; uric acid, 2.9 mg/dl; and osmolality, 259 mOsm/l (normal, 275 to 290). The plasma antidiuretic hormone (ADH) concentration was 4.3 pg/ml (normal, 0.3 to 4.2). Liver function parameters all were normal, as were cholesterol, triglyceride, glucose, protein, thyrotropin, free thyroxine, and basal cortisol concentrations. Urine osmolality was 490 mOsm/l (normal, 50 to 1,300). A chest radiograph, computed tomograms of the chest and abdomen, and magnetic resonance images of the brain all were normal except for the old cerebral infarct located in the left precentral gyrus.

Paroxetine-related SIADH was strongly implicated. Beginning on the day of admission, oral fluid restriction (1,000 ml/day) and intravenous normal saline (0.9%) were instituted. Paroxetine was discontinued, while other medications were continued. On the next morning, the serum sodium concentration was 120 mEq/l, and mental status had improved markedly. Serum sodium normalized over 5 days (Fig. 1), and the patient was discharged without further neurologic symptoms. During a follow-up period of 3 months, she has been in good clinical condition while maintaining a normal sodium concentration.

Discussion

SSRI-induced hyponatremia usually occurs in elderly patients, with onset during the first month of treatment (1, 2). Awareness of this possible diagnosis is important because serious hyponatremia may be mistaken for worsening of depression, as features of hyponatremia mimic certain depressive symptoms including nausea, weakness, fatigue, and confusion. Such hyponatremia has been reversed rapidly by discontinuing the drug and/or initiation of fluid restriction in almost all cases.

Although the precise mechanism of SSRI-induced hyponatremia is not established, SIADH is likely to be involved. Laboratory findings in our patient were highly suggestive of this syndrome, although the sodium concentration was not measured in the urine. As for paroxetine, a prospective study of 15 patients with depression by Fabian et al (4) disclosed hyponatremia in 6 (40%) at 2 weeks after initiation of the drug; in 3 of these patients, the disturbance was transient. They concluded that the syndrome might be responsible for hyponatremia because ADH concentrations in the hyponatremic patients were not appropriately suppressed in the presence of low serum osmolality.

The reason as to why the second exposure to paroxetine rather than the first induced severe hyponatremia in the present patient is not clear. To our knowledge, only one previously reported patient developed severe hyponatremia after resumption of paroxetine therapy (5). In our patient, asymptomatic transient hyponatremia occurred soon after the first exposure to paroxetine at 10 mg/day. This episode of mild hyponatremia was not rigorously proven to be secondary to paroxetine treatment, because other potential causative factors were not completely evaluated. Yet, considering the observations of Fabian et al (4), this early event in our patient is believed to have represented paroxetine-induced hyponatremia. Furthermore, resumption of medication at twice the initial dose of 10 mg/day may have accelerated early development of hyponatremia. Although a relationship between the dose of paroxetine and risk of hyponatremia has not been proven, a case of hyponatremia occurring during dose escalation in this drug class has been reported (6).

We should emphasize the importance of periodic measurements of serum sodium concentration in elderly patients receiving paroxetine or other SSRIs, whether for the first time or after interruption of treatment.

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