Case Report

Duloxetine-induced hyponatraemia in a patient with hypocortisolaemia

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Abstract

Duloxetine-induced hyponatraemia is a known adverse effect that can lead to potentially life-threatening complications. In addition, hypocortisolaemia is associated with the development of hyponatraemia. Here, we report a case of severe hyponatraemia rapidly presenting after duloxetine treatment in a patient with hypocortisolaemia. A 75-year-old man administered hydrocortisone for the treatment of hypocortisolaemia induced by a Rathke's cleft cyst was admitted for anorexia 3 days after the initiation of duloxetine therapy. Laboratory findings showed severe hyponatraemia, hypo-osmolality, concentrated urine, and increased urine sodium. Because the syndrome of inappropriate antidiuretic hormone was diagnosed, duloxetine was ceased. Following admission to the hospital, endocrinological analyses revealed mild hypocortisolaemia, possibly due to low adherence to hydrocortisone replacement therapy. By the sixth day after admission, the patient's hyponatraemia, serum osmolality, and urine osmolality had improved. This case suggests that health-care physicians should be aware of the possibility of duloxetine-related hyponatraemia, particularly in patients with hypocortisolaemia.

Keywords: Duloxetine, hypocortisolaemia, hyponatraemia, inappropriate ADH Syndrome

Introduction

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor used for the treatment of major depression and fibromyalgia.[1] Duloxetine-induced hyponatraemia is relatively rare and commonly occurs in elderly female patients.[2] Hypocortisolaemia decreases sodium reuptake, which can sometimes cause hyponatraemia.[3] In this article, we describe a case of severe hyponatraemia rapidly presenting after duloxetine treatment in a patient with hypocortisolaemia. To our knowledge, this is the first reported case of a patient with hyponatraemia induced by both duloxetine therapy and hypocortisolaemia. This case report is approved by the ethics committee of our hospital.

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Case History

A 75-year-old male patient complaining of anorexia and with a history of hypertension, hyperuricemia, and hypocortisolaemia was referred to our hospital by his family physician. According to the information obtained from the patient and his family physician, he complained of anorexia 1 day before admission. His weight was 63 kg, and the medications he was taking just before admission included 2.5 mg/day amlodipine, 20 mg/day olmesartan, 200 mg/day allopurinol, 10 mg/day hydrocortisone, and 20 mg/day duloxetine. About 1 year before admission, an endocrinologist at our hospital introduced hydrocortisone replacement therapy for the treatment of hypocortisolaemia induced by a Rathke's cleft cyst (RCC). According to his family physician, duloxetine was prescribed for lethargy 3 days before admission. His serum sodium level at admission was extremely low at 115 mEq/L (normal, 136–145). Other clinical laboratory findings showed a serum urea nitrogen level of 21.4 mg/dL (normal, 9.0–22.0), serum creatinine level

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of 1.06 mg/dL (normal, 0.5–1.1), serum osmolality of 242 mOsm/L (normal, 280–290), simultaneous urine osmolality of 585 mOsm/L (normal, 200–800), and urine sodium of 29 mEq/L (normal, less than 10). Endocrinological analyses revealed a 3.6-μg/dL (normal, 3.7–19.4) serum cortisol level and 2.0 pg/mL (normal, 7.2–63.3) serum adrenocorticotropic hormone (ACTH) level. According to his family physician, his serum sodium level 3 days before admission was 135 mEq/L. His other laboratory findings were within the normal range. Other than duloxetine, his medications were not modified. Based on laboratory reports, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was diagnosed. Because we assumed that his hyponatraemia was associated with both duloxetine and mild hypocortisolaemia, duloxetine was ceased. The severe hyponatraemia was then treated with oral fluid restriction and oral furosemide (20 mg/day). According to the information obtained from the patient, he showed low adherence and skipped his hydrocortisone about 3 times/week. Therefore, we explained the importance of hydrocortisone replacement therapy to prevent the recurrence of hyponatraemia. By the fourth day after admission, his hyponatraemia had improved to 134 mEq/L, and serum and urine osmolality also improved. On the next day, oral fluid restriction and oral furosemide were discontinued because he did not complain of anorexia. By the 10th day after admission, his hypocortisolaemia improved to 4.5 μg/dL, whereas his serum ACTH remained low at 2.0 pg/mL [Table 1]. He was discharged the next day. Following discharge, the patient demonstrated high adherence to his hydrocortisone therapy. To date, medical examinations have shown no evidence of either symptomatic hyponatraemia or hypocortisolaemia.

Discussion

Although the mechanism contributing to duloxetine-related hyponatraemia is unclear, duloxetine inhibits the reuptake of both serotonin and norepinephrine, which can stimulate ADH secretion.[4] Therefore, duloxetine-related hyponatraemia is likely associated with SIADH, and laboratory findings on admission corresponded with the SIADH diagnostic criteria. Based on the Naranjo scale,[5] SIADH was likely related to duloxetine therapy (score 4). The risk factors for duloxetine-related hyponatraemia include advanced age, female patients, lower body weight, lower baseline serum sodium, and treatment with medicines that can cause hyponatraemia.[2] Recently, it has been reported that renal involvement of autoimmune diseases, such as Soren's syndrome, could also be a risk factor for duloxetine-induced hyponatraemia.[6] Our patient had two risk factors for duloxetine-related hyponatraemia, including advanced age and lower baseline serum sodium. Because endocrinological analyses at admission revealed mild hypocortisolaemia at 3.6 μg/dL, the lower baseline serum sodium level might have been caused by mild hypocortisolaemia.

The mechanism underlying hyponatraemia caused by hypocortisolaemia is probably related to the reduction in sodium reuptake. RCCs can cause pituitary dysfunction associated with a disrupted ACTH–cortisol axis. Given that cortisol promotes sodium reuptake in the collecting tubules,[3] hyponatraemia is presumably caused by decreased sodium reuptake due to hypocortisolaemia. This evidence suggests that severe hyponatraemia developed because of both duloxetine-induced SIADH and hypocortisolaemia through complementary and synergistic mechanisms. In our case, hypocortisolaemia is possibly due to low adherence to hydrocortisone replacement therapy. It has been reported that more than 50% of patients treated with pharmacotherapy for chronic diseases may have difficulty adhering to their pharmacotherapy for longer than 6 months.[7] Adherence to pharmacotherapy generally depends on the medical practitioner's instructions.[8] Our patient was treated with hydrocortisone for about 1 year, and he showed good compliance with his hydrocortisone replacement therapy after receiving our instructions. Therefore, primary care physicians should confirm the adherence to hydrocortisone replacement therapy before duloxetine is initiated in patients treated with hydrocortisone. It has been reported that mirtazapine may have lower risk for hyponatraemia when compared with other selective serotonin reuptake inhibitors.[9] If low adherence to hydrocortisone replacement therapy is suspected, pharmacists should provide pharmaceutical instructions to improve patient's adherence, and primary care physicians should consider an alternative therapy with other antidepressants, such as mirtazapine.

This case highlights the development of severe hyponatraemia rapidly presenting after duloxetine treatment in a patient with hypocortisolaemia due to low adherence to hydrocortisone replacement therapy. Therefore, this case suggests that both duloxetine-induced SIADH and hypocortisolaemia caused severe

Table 1: Patient laboratory findings

Events		Duloxetine started	Duloxetine discontinued					
Days after admission		−3	0	2	4	10	25	53
Laboratory data	Normal range							
serum sodium (mEq/L)	136-145	135	115	120	134	137	139	140
SOsm* (mOsm/L)	280-290		242		280			
UOsm† (mOsm/L)	200-800		585		278			
U-Na‡ (mEq/L)	<10		29		35			
Serum cortisol (μg/dL)	3.7-19.4		3.6			4.5	6.2	6.7
Serum ACTH§ (pg/mL)	7.2-63.3		2.0			2.0	2.0	2.0

*Serum osmolality, †Urine osmolality, ‡Urine sodium, §Adrenocorticotropic hormone

hyponatraemia through complementary and synergistic mechanisms. To evaluate the risk of hyponatraemia, primary care physicians should confirm the adherence to hydrocortisone replacement therapy before duloxetine is initiated in patients receiving hydrocortisone therapy. If low adherence to hydrocortisone replacement therapy is suspected, primary care physicians should consider an alternative therapy with other antidepressants, such as mirtazapine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his clinical information to be reported in the journal. The patient understand that his name and initial will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Key Messages

Our case suggests that both duloxetine-induced SIADH and hypocortisolaemia caused severe hyponatraemia through complementary and synergistic mechanisms. Careful attention should be paid to the potential risk of hyponatraemia when duloxetine is administered, particularly in patients with low adherence to hydrocortisone replacement therapy.

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Conflicts of interest

There are no conflicts of interest.

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