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Rapid-onset hyponatremia and delirium following duloxetine treatment for postherpetic neuralgia

Case report and literature review

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Abstract

Rationale: Hyponatremia following duloxetine treatment has been reported in patients with major depressive disorder, fibromyalgia, diabetic neuropathy, or sciatic pain. The manifestations of duloxetine-induced hyponatremia are varying in different individuals. The overall prognosis for this type of hyponatremia is favorable if properly managed.

Patient concerns and diagnoses: Herein, we reported rapid-onset hyponatremia and delirium in an older patient after 2 doses of duloxetine, which was used to control his postherpetic neuralgia. Laboratory examinations revealed a rapid decline in serum sodium level and indicated the possibility of syndrome of inappropriate antidiuretic hormone (SIADH).

Interventions: Discontinuation of duloxetine, restriction of water intake, and intravenous supplement of normal saline were adopted to manage the hyponatremia.

Outcomes: Serum concentration of sodium gradually normalized following aforementioned strategies.

Lessons: Special attention to the electrolyte abnormality is recommended in old patients undergoing duloxetine treatment.

Abbreviations: COPD = chronic obstructive pulmonary disease, CSF = cerebrospinal fluid, SIADH = syndrome of inappropriate antidiuretic hormone, SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors.

Keywords: duloxetine, hyponatremia, postherpetic neuralgia

1. Introduction

Hyponatremia is a common electrolyte abnormality and has potentially life-threatening complications.[1] Hyponatremia caused by antidepressants treatment is also frequently observed in clinical practice.[2] Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine) have been widely reported to induce hyponatremia in susceptive individuals.[2–4] However, inadequate attention has been paid to this adverse event caused by duloxetine in clinical practice.

To date, sporadic case studies have reported duloxetine-associated hyponatremia in patients with major depressive disorder, fibromyalgia, diabetic neuropathy, or sciatic pain,[5–18] but not in patients with postherpetic neuralgia. Postherpetic neuralgia is an intractable sequela of herpes zoster and greatly impacts the life quality.[19] Topical and systemic medications can be used to control this condition according to the severity of neuropathic pain.[20] Anticonvulsants, tricyclic antidepressants, and the opioid analgesics are the recommended systemic agents for patients with severe pain.[20] As a SNRI antidepressant, duloxetine has a satisfying effect in alleviating the accompanying somatic pain in depressed patients.[21] Moreover, duloxetine may also be effective in resolution of painful neuropathy and different types of chronic pain.[22] However, duloxetine is only approved to treat depression in China.

Herein, we present a case of rapid-onset hyponatremia in an old patient with postherpetic neuralgia, who was off-label treated by duloxetine. This patient rapidly developed weakness, lethargy, and delirium-like symptoms during hyponatremia and recovered after duloxetine discontinuation, water restriction, and intravenous supplement of normal saline. Moreover, this article briefly reviews the documented cases of duloxetine-associated hyponatremia and summarized the demographic and clinical characteristics of these patients.

2. Case presentation

A 78-year-old male patient was admitted to our hospital because of debilitating skin pain for 3 weeks. On admission, scattered rashes could be visually noted in the right side of the forehead, the upper eyelid, and the periorbital skin. He complained drooping eyelid, restricted eye-movement and double vision for 2 weeks. Given the existence of right oculomotor paralysis, lumber puncture was timely performed after excluding contraindications and obtaining

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informed consent. Examination of the cerebrospinal fluid (CSF) indicated an elevated count of white blood cell (0.041, normal: 0–0.005) and increased protein (0.60, normal: 0.15–0.45). Laboratory investigations of routine blood test, liver function, renal function, electrolyte concentration, thyroid function, cortical hormone, tumor biomarkers, and autoimmune antibodies were all within the normal limits. His past medical history included hypertension and chronic obstructive pulmonary disease (COPD). He was taking amlodipine tablets and tiotropium bromide power for inhalation to control these diseases.

Accordingly, herpes zoster with accompanying oculomotor paralysis was diagnosed. Intravenous acyclovir and dexamethasone was administrated. To cope with his skin pain, gabapentin was gradually titrated to 300 mg 3 times per day. An ophthalmologic consultation indicated keratitis and ganciclovir eye gel was prescribed. Nearly 2 weeks following this treatment strategy, lumber puncture was performed again and reexamination of the CSF returned to normal. Although this patient felt his right eye movement became flexible, skin pain around the lesion did not significantly alleviate. To relieve his pain, duloxetine in a daily dose of 60 mg was added. The other medications were kept the same as before. However, after 2 doses of duloxetine, this patient began to feel fatigued and appeared to be poorly orientated and lethargic. When falling asleep, he would wave his arms and randomly grope. When woken up, he explained these behaviors as catching chickens or carrying a bucket. Immediate blood electrolyte was performed and indicated hyponatremia (125, normal: 132–145 mmol/L) and hypochloridemia (89, normal: 90–108 mmol/L). Serum osmolality was 254 mOsm/L and urine osmolality was 430 mOsm/L. No indications of new-onset infection were discovered. Reexamination of renal function was also normal. Cranial magnetic resonance imaging revealed no significant findings. According to the laboratory results, SIADH was considered. His delirium-like symptoms were considered to be secondary to hyponatremia. Because hyponatremia emerged rapidly following duloxetine treatment, duloxetine was thought to be the culprit and subsequently discontinued. Meanwhile, daily water restriction and intravenous supplement of normal saline was initiated. Within 1 week after duloxetine withdrawal, his serum sodium concentration returned to normal level (the dynamic change of serum sodium concentration was shown in Figure 1). Symptoms of lethargy and weakness also improved. No recurrence of hyponatremia was detected in follow-up visits.

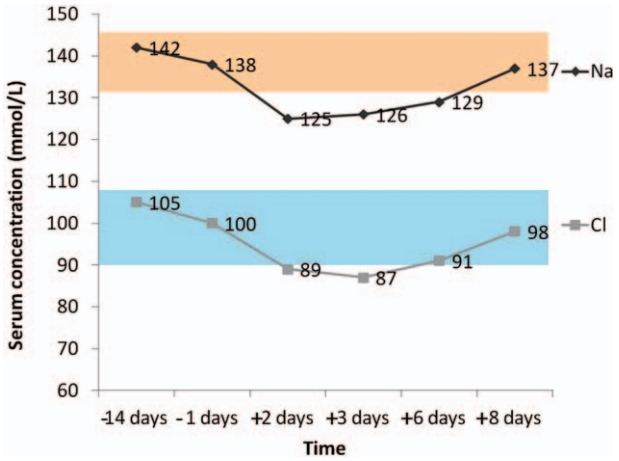

Figure 1. Dynamic monitoring of serum concentration of sodium and chloride in the patient. "−" refers to "before the onset of hyponatremia", "+" refers to "after the onset of hyponatremia", the pink area represents the reference range of serum sodium concentration, and the blue area represents the reference range of serum chloride concentration.

This case study obtained approval from the Institute Ethical Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. An informed consent for publication of the case details was provided by our patient and his guardians.

3. Discussion

In this case study, we first present an old male patient with postherpetic neuralgia, who developed hyponatremia following duloxetine treatment. Before taking duloxetine, the baseline serum level of sodium was normal, but declined rapidly after ingesting only 2 doses of duloxetine. His condition improved within 1 week after duloxetine discontinuation, water restriction, and supplement of normal saline. According to the Naranjo scale for evaluating the probability of adverse drug effects, the relationship of duloxetine and hyponatremia in our patient was "probable."[23]

According to the previous reports, SIADH was the most mentioned explanation accounting for duloxetine-induced hyponatremia. The exact molecular mechanism of SIADH caused by antidepressants remains unclear. As a dual-action antidepressant, duloxetine enables to increase the concentrations of serotonin and norepinephrine, and further possibly stimulate the secretion of antidiuretic hormone.[24] Several factors, such as older age, female gender, concomitant use of (thiazide) diuretics, a history of hyponatremia, low weight (<60 kg), psychosis, have been identified to increase the risk of hyponatremia induced by antidepressants.[3,4,25] In addition, COPD was also possibly one of the respiratory causes for SIADH.[17] Therefore, the older age (78-year-old), low weight (48 kg), and history of COPD could be the extra risk factors for our patient.

To better understand the features of duloxetine-related hyponatremia, we further reviewed the published relevant case reports and summarized the demographic and clinical characteristic of these individuals. As demonstrated in Table 1, only 26.3% (5/19, including our case, similarly hereinafter) of all patients was male, and 36.8% (7/19) was <65 years old. Most patients with duloxetine treatment are depressed and a few of them have neuropathic pain or fibromyalgia. Comorbid physical conditions included diabetic mellitus, hypertension, cardiovascular/cerebrovascular diseases, pneumonia, neurologic diseases, and even cancers. Most concomitant drugs were taken for these chronic diseases, and only 1 patient took diuretics (trichlormethiazide). The doses of duloxetine were different, and could be as low as 20 mg/daily and as high as 120 mg/daily. Hyponatremia could rapidly emerge after 2 days of duloxetine treatment, or delayed for several weeks or even months. Symptoms of duloxetine-induced hyponatremia were varying, including fatigue, weakness, lethargy, headache, nausea, dizziness, altered mental status and seizure as well. Some of these symptoms were mild and atypical, thus would be confused with the primary diseases and even be neglected. The average falling range of serum sodium concentration was 20.8 mmol/L in patients with duloxetine-induced hyponatremia. The overall prognosis was favorable in all patients after duloxetine withdrawal, water restriction, intravenous or oral supplement of sodium, or using diuretics (furosemide). It could be helpful for clinicians to better recognize and treat hyponatremia caused by duloxetine when getting hold of the aforementioned information.

Table 1

Demographic and clinical profiles of patients with duloxetine-associated hyponatremia.

No.	Sex	Age	Diagnosis	Physical diseases	Dose and frequency of duloxetine treatment	Other medication/s	Duration of duloxetine treatment	Symptoms	Baseline serum level of sodium, mmol/L	The lowest serum level of sodium, mmol/L	Serum osmolality, mOsm/L	Urine osmolality, mOsm/L	Treatment	References
1	Female	35	Depression	—	90 mg daily	Lorazepam, zopiclone	4 wk	Fatigue, muscle weakness	146.3	122.1	269	—	Decrease the dose, water restriction	5
2	Female	70	Depression	Hypertension	120 mg daily	Lorazepam, zopiclone	6 wk	Fatigue, lethargy	139.8	120.3	250	—	Discontinuation, water restriction, dietary sodium	
3	Female	45	Depression	—	120 mg daily	Lorazepam, zopiclone	4 wk	Headache, fatigue, lethargy	150.0	118.2	265	—	Discontinuation, water restriction, salt tablet	
4	Male	67	Depression	—	120 mg daily	Lorazepam, zopiclone	5 wk	Headache, lethargy	148.5	120.7	270	—	Discontinuation, water restriction	
5	Male	56	Depression	—	90 mg daily	Lorazepam, zopiclone	4 wk	Headache, fatigue, muscle weakness, lethargy	142.4	118.4	252	—	Discontinuation, water restriction, salt tablets	
6	Female	68	Neuropathic pain	Peritoneal carcinoma	60 mg daily	Gabapentin, verapamil, lopressor, oxycodone, zolpidem, warfarlin	2 d	Fatigue, nausea	138	112	245.3	703	Discontinuation, water restriction, intravenous sodium, furosemide	6
7	Female	48	Depression	—	60 mg daily (30 mg BID)	—	2 d	Seizure	—	103	215	450	Discontinuation, water restriction,	7
8	Female	50	Depression	—	60 mg daily	Ziprasidone	10 d	Polyuria, polydipsia, seizure, coma	—	116.5	249	—	Discontinuation, water restriction, intravenous normal saline	8
9	Female	74	Sciatic pain	Hypertension	60 mg daily	Pregabalin, tramadol, acetaminophen, aspirin, β and angiotensin receptor blockers	12 d	Headache, nausea, vomit	—	112	248	328	Discontinuation, slow intravenous hypertonic saline followed by normal saline	9
10	Female	86	Depression	Hypertension, vertigo, insomnia	20 mg daily	Trichlormethiazide, doxazosin, tocopherol nicotinate, oxybutynin, diphenidol, bethahistine, domperidone, trizolam, lorazepam	6 d	Disorientation, nausea	142	116	239	385	Discontinuation, water restriction, oral furosemide, oral sodium chloride	10
11	Male	75	Sensorimotor polyneuropathy, depressive symptoms	—	30 mg daily	—	3 d	Lethargy, headache, nausea	138	118	245.7	578.3	Discontinuation, intravenous hypertonic saline	11
12	Male	58	Depression	Pneumonia	30 mg daily	Amicacin sulfate	6 d	—	135.1	122	263	394	Discontinuation, water restriction, intravenous hypertonic saline	12
13	Female	66	Depression	Coronary artery disease, dyslipidemia, gastroesophageal reflux disease, hiatal hernia, hypertension, partial complex seizures, peripheral vascular disease, restless leg syndrome, sleep apnea, tinnitus, transient ischemic attack, vertigo	60 mg daily	Amlodipine, aspirin, clopidogrel, gabapentin, hydrocodone Acetaminophen, olmesartan, pantoprazole, phenytoin, ropinirole, simvastatin	Almost 3 y	Lethargy, muscle weakness, nausea, altered mental status	—	129, with sodium supplements	—	243	Discontinuation, water restriction, sodium supplement	13

(*continued*)

Table 1

(continued).

No.	Sex	Age	Diagnosis	Physical diseases	Dose and frequency of duloxetine treatment	Other medication/s	Duration of duloxetine treatment	Symptoms	Baseline serum level of sodium, mmol/L	The lowest serum level of sodium, mmol/L	Serum osmolality, mOsm/L	Urine osmolality, mOsm/L	Treatment	References
14	Female	85	Depression	—	60 mg daily (30 mg BID)	—	2 d	Somnolence, facial paralysis, abnormal gait	134	120	272	—	Discontinuation, water restriction	14
15	Female	85	Depression	—	30 mg daily	—	6 d	coma	—	107	234	310	Discontinuation, intravenous saline	15
16	Female	48	Fibromyalgia	Systemic lupus erythematosus, type 2 diabetes mellitus, hypertension, migraine, gastroparesis, mitral valve prolapsed, hypothyroidism, hyperprolactinemia	—	Naratriptan, amitriptyline, cabergoline, propranolol, sitagliptin, meloxicam, hydroxychloroquine, pravastatin, lansoprazole, levothyroxine, vitamine D, azelastine, polyethylene glycol, aspirin	>3 mo	Headache, nausea, vomit, confusion	137	120	—	—	Intravenous hypertonic saline, furosemide,	16
17	Female	76	Fibromyalgia	Type 2 diabetes mellitus, hypertension	30 mg daily	Aspirin, pantoprazole, polyethylene, glycol, quinapril	2 d	Nausea	132	118	254	415	Discontinuation, water restriction, salt tablets	17
18	Female	76	Diabetic neuropathy	Diabetes mellitus	30 mg daily	Metoprolol, metformin	3 d	Nausea, vomiting, dizziness, weakness, confusion	—	113	236	332	Discontinuation, intravenous hypertonic saline	18

To conclude, we depict a case of rapid-onset hyponatremia following duloxetine treatment in an old male patient with postherpetic neuralgia. Our work indicates the importance of continuous monitoring serum electrolyte when prescribing duloxetine, especially in patients with predisposing factors.

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