JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
CASE REPORT

Rapid onset of syndrome of inappropriate antidiuretic hormone secretion induced by duloxetine in an elderly type 2 diabetic patient with painful diabetic neuropathy

Shinji Kamei*, Hideaki Kaneto, Akihito Tanabe, Shintaro Irie, Yurie Hirata, Masashi Shimoda, Kenji Kohara, Tomoatsu Mune, Kohei Kaku

Division of Diabetes, Metabolism and Endocrinology, Kawasaki Medical School, Kurashiki, Japan

Keywords
Cytochrome P450, Duloxetine, Syndrome of inappropriate antidiuretic hormone secretion

***Correspondence**
Shinji Kamei
Tel.: +81-86-462-1111
Fax: +81-86-464-1046
E-mail address: s.kamei@med.kawasaki-m.ac.jp

J Diabetes Invest 2015; 6: 343–345

doi: 10.1111/jdi.12301

ABSTRACT

Diabetic neuropathy is the most common diabetic complication. Duloxetine, a serotonin noradrenaline reuptake inhibitor (SNRI), is widely used for the treatment of diabetic painful neuropathy (DPN) because of the efficacy and safety profile. Syndrome of inappropriate antidiuretic hormone secretion, which is strongly associated duloxetine, is a rare but occasionally life-threatening adverse effect. Here, we report a case of syndrome of inappropriate antidiuretic hormone secretion that rapidly developed after starting duloxetine in an elderly Japanese female type 2 diabetes mellitus patient. Furthermore, we discuss the possible relationship between the onset of syndrome of inappropriate antidiuretic hormone secretion and the gene polymorphism of cytochrome P450 isoform 1A2 and 2D6, both of which are responsible for duloxetine metabolism.

INTRODUCTION

Diabetic neuropathy is the most common diabetic complication, and 10–20% patients with diabetic neuropathy suffer pain[1]. Duloxetine is a serotonin noradrenaline reuptake inhibitor (SNRI) that has often been used for painful diabetic neuropathy in many countries because of the efficacy and favorable adverse-effect profile[2]. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by inappropriate antidiuretic hormone (ADH) release and hyponatremia. SIADH is a frequent cause of hyponatremia, with a wide spectrum of clinical manifestation, from chronic and asymptomatic to acute and lethal conditions. In addition, SIADH could be induced by several drugs. It is well known that some fatal drug poisoning is closely associated with poorly metabolized type of cytochrome P450 (CYP)[3]. Here, we report a case of SIADH that developed just after starting duloxetine in an elderly diabetic patient, which was successfully treated, and discuss the possible mechanism of the onset of SIADH associated with the CYP1A2 and 2D6 polymorphism.

Received 27 August 2014; revised 30 September 2014; accepted 13 October 2014

CASE REPORT

An 80-year-old Japanese diabetic woman with diabetic neuropathy complained about a painful sensation and numbness of both legs. She had been taking oral hypoglycemic agents for diabetes with suboptimal glycemic control for more than a decade before admission. To reduce such symptoms, she started taking duloxetine (20 mg/day) in May 2012. The next morning after starting duloxetine treatment, she felt an uncomfortable sensation, and then had marked nausea and poor appetite. She was hospitalized for careful examination. On admission, her bodyweight was 45.5 kg and her height was 148 cm (body mass index was 23.3 kg/m^2). She was afebrile, but slightly drowsy. There was no jugular venous distention and no pretibial pitting edema. Her blood pressure was 120/84 mmHg and pulse rate was 101 b.p.m. Neurological examination showed no muscle weakness in the proximal lower limbs. Deep tendon reflex was almost absent in the bilateral lower extremities. Chest X-ray showed no overt consolidations and no cardiomegaly. Computed tomography of the brain showed no obvious abnormalities. Glycated hemoglobin was 6.9% and fasting plasma glucose was 156 mg/dL. Serum sodium and chloride

concentration was 118 mEq/L and 84 mEq/L, respectively. Renal function test showed no abnormalities (serum creatinine 0.39 mg/dL; urea nitrogen 12 mg/dL; estimated glomerular filtration fate 114.2 mL/min/1.73 m^2). Other electrolytes, whole blood count and liver function were normal. Thyroid-stimulating hormone and free thyroxine were 2.4 μIU/mL, 3.04 pg/mL, 1.19 ng/dL, respectively. Adrenocorticotropic hormone and cortisol levels were within the normal range. Urine sodium was 128 mEq/L and potassium was 40 mEq/L. Serum ADH was elevated to 12.5 pg/mL (normal range 0.3–3.5 pg/mL). Urine was concentrated at 539 mOsm/kgH_2O compared with a plasma osmolality of 252 mOsm/kgH_2O. Excessive urinary sodium excretion persisted despite severe hypotonic hyponatremia. We excluded all other potential causes of hyponatremia, such as liver cirrhosis, congestive heart failure, hypotonic dehydration and malignancy-associated diseases.

Given these findings, we diagnosed the patient as duloxetine-induced SIADH. We stopped duloxetine, started the intravenous saline infusion and restricted water intake. The serum sodium level gradually increased to 130 mEq/L at day 3 of hospitalization and normalized at day 5. The ADH level was reduced to <1.2 pg/mL, and her consciousness level was recovered. The symptoms of her painful peripheral neuropathy showed no progression. At day 13, the patient was discharged without any symptom of SIADH. At the last follow up in December 2013, she was doing well and in good glycemic control without symptoms of SIADH.

DISCUSSION

Duloxetine has a weak affinity for the dopamine transporter and a insignificant affinity with other neurotransmitter receptors, including muscarinic, histamine and γ-amino butyric acid. Therefore, it has been thought that duloxetine is safe and tolerable compared with other antipsychotic agents. Serious adverse events were not common with both short- and long-term duloxetine treatment. It has been reported, however, that SIADH could be induced by duloxetine, and that hyponatremia is usually observed a few days after initiation of duloxetine[4]. In addition, it has been suggested that the risk factors for hyponatremia include older age, female sex, lower body mass index and lower serum sodium level. The present case had two risk factors, older age and female sex, and thereby we should have paid more careful attention.

SIADH is one of the most frequent causes of euvolemic hyponatremia. SIADH is defined by decreased serum osmolality, coexisting urine osmolality above 100 mOsm/kg, urinary sodium above 40 mmol/L, euvolemia and the absence of other causes for hyponatremia[5]. The definitive diagnosis is obtained through an exclusion algorithm of these causative conditions[5]. Our patient satisfied that criteria for SIADH. Mild chronic hyponatremia is often asymptomatic, but an acute (within 48 h) decrease in serum sodium concentration to below 120 mEq/L is associated with serious neurological complications including confusion, hallucinations, seizures and coma, and acute severe hyponatremia is potentially life-threatening compared with hyponatremia, with a chronic or slow progression. The present case was in this life-threatening condition at admission, and thus we had to appropriately diagnose and promptly start treatment for it. SIADH associated with duloxetine and other SNRIs is relatively uncommon, but potentially has severe adverse effects with an unknown frequency of occurrence. It has been proposed that the increase of noradrenalin and serotonin levels in the posterior lobe of the pituitary gland could explain, at least in part, the mechanism by which duloxetine and SSRIs induce SIADH[6,7]. Furthermore, it is likely that duloxetine can cross the blood–brain barrier because of the low molecular weight (molecular weight 334) and high liposolubility.

It is known that some fatal drug poisoning is closely associated with a poorly metabolized type of CYP[3]. Therefore, to explore the possible reason why SIADH occurred, we examined the CYP metabolism of the patient's regular medication before admission, and her gene polymorphism of CYP isoform 1A2 and 2D6, both of which are responsible for duloxetine metabolism[8,9]. There was no medication related to CYP1A2 or CYP2D6 before admission (Table 1). CYP2D6 and CYP1A2 are genetically polymorphic, and are associated with large inter-individual variations in therapeutic efficacy and drug toxicity[10]. After obtaining written informed consent, we examined CYP2D6 and CYP1A2 using polymerase chain reaction–restriction fragment length polymorphism and invader genotyping assay. As shown in Table 2, both CYP1A2 and 2D6 were the heterozygous phenotype; CYP1A2 had the wild-type/poor metabolizer phenotype (*1C: -3860G>A) and CYP2D6 had the wild-type/poor metabolizer phenotype (*5: gene deleted). These phenotypes indicate the intermediate metabolizer of duloxetine,

Table 1 | Cytochrome P450 metabolism of regular medication in this subject before admission

Generic name	Main CYP metabolism
Glimepiride	CYP2C9
Voglibose	Not metabolized
Amlodipine besilate	CYP3A4
Ezetimibe	Not metabolized
Olmesartan medoxomil	Not metabolized

CYP, cytochrome P450.

Table 2 | Gene polymorphism of cytochrome P450 isoform 1A2 and 2D6 in the patient

	Genotype	Haplotype
CYP1A2	*wt/*1C*	IM
CYP2D6	*wt/*5*	IM

**1C*, (-3860G>A); **5*, gene deletion; CYP1A2, cytochrome P450 isoform 1A2; CYP2D6, cytochrome P450 isoform 2D6; IM, intermediate metabolizer; *wt*, wild type.

which shows a mild to moderate decline of duloxetine metabolism[11]. We failed to evaluate the patient's serum concentration of duloxetine, but we assume that this was one of the reasons why duloxetine induced SIADH, although its precise association remains unknown.

To our best knowledge, this is the first report showing a case of SIADH that rapidly developed just after starting duloxetine, and discussing the possible relationship between the onset of SIADH and the CYP1A2 and 2D6 polymorphism. In conclusion, we should be aware that duloxetine could induce SIADH when we use it for painful diabetic neuropathy.

ACKNOWLEDGMENTS

The authors declare no conflict of interest.

REFERENCES

1. Boulton AJM, Rayaz AM, Arezzo JC, *et al*. Diabetic somatic neuropathies. *Diabetes Care* 2004; 27: 1458–1486.
2. Attal N, Cruccu G, Baron R, *et al*. EFNS guidelines on the pharmacological management of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; 17: 1113–1123.
3. Jornil J, Nielsen TS, Rosendal I, *et al*. A poor metabolizer of both CYP2C19 and CYP2D6 identified by mechanistic pharmacokinetic simulation in a fatal drug poisoning case involving venlafaxine. *Forensic Sci Int* 2013; 226: e26–e31.
4. Maramattom BV. Duloxetine-induced syndrome of inappropriate antidiuretic hormone secretion and seizures. *Neurology* 2006; 66: 773–774.
5. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; 356: 2064–2072.
6. Anderson IK, Martin GR, Ramage AG. Central administration of 5-HT activates 5-HT1A receptors to cause sympathoexcitation and 5-HT2/5-HT1C receptors to release vasopressin in anaesthetized rats. *Br J Pharmacol* 1992; 107: 1020–1028.
7. Leibowitz SF, Eidelman D, Suh JS, *et al*. Mapping study of noradrenergic stimulation of vasopressin release. *Exp Neurol* 1990; 110: 298–305.
8. Skinner MH, Kuan HY, Pan A, *et al*. Duloxetine is both an inhibitor and a substrate of cytochrome P450 2D6 in healthy volunteers. *Clin Pharmacol Ther* 2003; 73: 170–177.
9. Lantz RJ, Gillespie TA, Rash TJ, *et al*. Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. *Drug Metab Dispos* 2003; 31: 1142–1150.
10. Braam W, Keijzer H, Struijker BH, *et al*. CYP1A2 polymorphisms in slow melatonin metabolisers: a possible relationship with autism spectrum disorder? *J Intellect Disabil Res* 2013; 57: 993–1000.
11. Chiba K, Kato M, Ito T, *et al*. Inter-individual variability of in vivo CYP2D6 activity in different genotypes. *Drug Metab Pharmacokinet* 2012; 27: 405–413.