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

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INTRODUCTION
Diabetic neuropathy is the most common diabetic complication, and 10–20% patients with diabetic neuropathy suffer pain1. 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 profile2. 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.

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/m²). 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 rate 114.2 mL/min/1.73 m²). 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 0.3–1.2 pg/mL), and her consciousness level was recovered. The symptoms of her painful peripheral neuropathy were 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. 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. The definitive diagnosis is obtained through an exclusion algorithm of these causative conditions. 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 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. 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. 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. 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,
which shows a mild to moderate decline of duloxetine metabolism. 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.

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REFERENCES
1. Boulton AJM, Rayaz AM, Arezzo JC, et al. Diabetic somatic neuropathies. Diabetes Care 2004; 27: 1458–1486.
2. Atta N, Crucu 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.