INTERNAL MEDICINE

□ CASE REPORT □

Acute-Onset Type 1 Diabetes that Developed During the Administration of Olanzapine

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Abstract

The patient was 32-year-old man, who received olanzapine for schizophrenia and developed polyuria and thirst without drinking soft-drinks after 4 months. Five months after the initiation of treatment, he developed diabetic ketoacidosis (blood glucose: 490 mg/dL, HbA1c: 15.5%). He was diagnosed with type 1 diabetes (glutamic acid decarboxylase (GAD)-Ab: 5.6 U/mL, IA-2 Ab: 5.9 U/mL, fasting C-peptide: 0.12 ng/mL) and was put on intensive insulin therapy. At four months after the onset of 1A diabetes, he experienced a honeymoon phase that was sustained until the 40th month of treatment. We hypothesize that the administration of olanzapine to a patient with pre-type 1A diabetes induced marked hyperglycemia and accelerated the onset of type 1A diabetes.

Introduction

Serotonin-dopamine antagonists (SDAs) are effective for treating schizophrenia (1, 2). These compounds are listed in the American Psychological Association (APA) guidelines as the first choice in acute phase treatment (3). However, one side effect of these SDAs is glucose intolerance (4-9), which occasionally causes a hyperglycemic crisis, and a few fatal cases have been reported (5, 10-12). There are no reports of these drugs being associated with the onset of type 1A diabetes.

Meanwhile, type 1A diabetes causes a decrease in endogenous insulin secretion due to pancreatic β-cell dysfunction via an immunological mechanism (13, 14). As the damage to the pancreatic β-cells progresses, the activity of the remaining β-cells decreases by approximately 20-30%, causing hyperglycemia and the onset of type 1A diabetes (15-17). However, even before this stage, exposure to severe stress can cause hyperglycemia and accelerate the onset of type 1A diabetes (18, 19). In the present report, we describe a case of type 1A diabetes that was triggered by the administration of SDAs during the treatment of schizophrenia.

Case Report

The patient was a 32-year-old man with no history of obesity and no family history of diabetes. At 23 years of age, he had developed schizophrenia and underwent treatment. He did not suffer from eating disorders during the clinical course of schizophrenia, and blood tests revealed no glucose intolerance or gastrointestinal disorders. More recently, the patient received risperidone (3 mg/day) and fluvoxamine maleate (50 mg/day). Because of the varied improvement of the patient's symptoms, the treatment was changed to olanzapine (5 mg/day) when the patient was 31 years and 4 months of age. Quetiapine (25 mg/day) was added at 1 month after the start of olanzapine treatment. A marked improvement in the psychiatric symptoms was observed 4 months later, when olanzapine was withdrawn and the patient was switched to quetiapine (50 mg/day). However, approximately 3 months after the initiation of olanzapine, the subject developed polyuria, polydipsia, oral dryness (he drank approximately 4 L of water per day) despite abstaining from soft-drink consumption. Four months after the

Table 1.   Laboratory Findings on Admission.

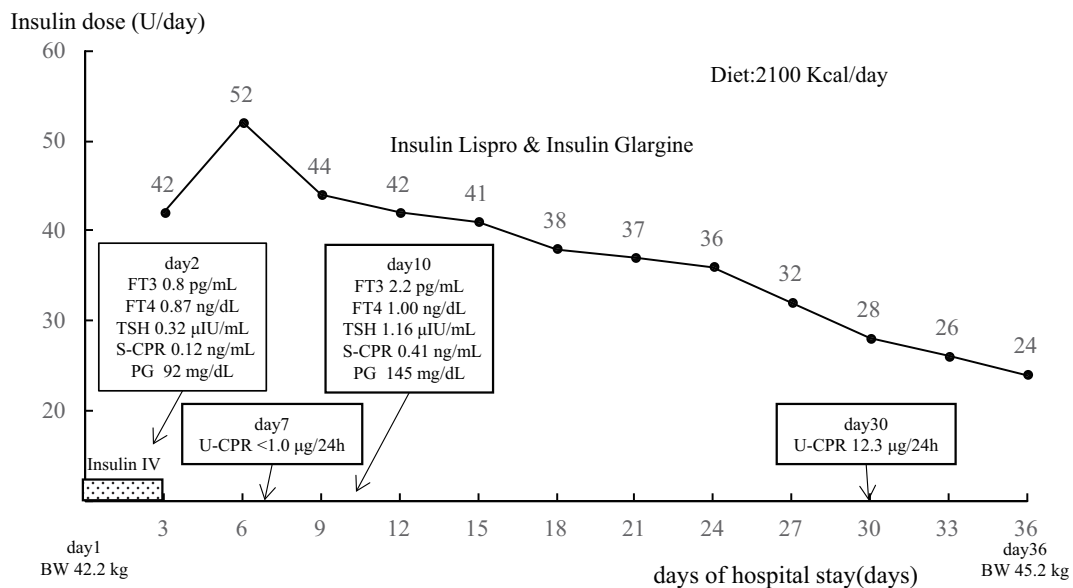| <Blood gas analysis>		<Biochemical>			
pH	7.25	Tp	7.4g/dL	AMY	36U/L
pCO$_2$	21.0mmHg	Alb	4.9g/dL	CK	41U/L
pO$_2$	123.6mmHg	BUN	13.3mg/dL	CRP	0.2mg/dL
HCO$_3^-$	9.0mmol/L	UA	6.6mg/dL	P-Glu	490mg/dL
BE	-15.7mml/L	Cre	0.4mg/dL	HbA1c (NGSP)	15.5%
		Na	134mEq/L	Fasting C-peptide	0.12ng/mL
<Complete blood count>		Cl	95mEq/L	※P fasting-Glu 221mg/dL	
WBC	10,500/μL	K	3.9mEq/L		
Hb	16.5g/dL	Ca	9.4mg/dL	FT3	0.8pg/mL
Hct	49.3%	i-P	3.9mg/dL	FT4	0.87ng/dL
PLT	21.1×10^4/μL	T-Bil	0.5mg/dL	TSH	0.32μIU/mL
		D-Bil	0.1mg/dL	TgAb	<0.3U/mL
<Urinalysis>		AST	13IU/L	TPOAb	<0.3U/mL
PH	5.0	ALT	14IU/L	TRAb	6.2%
protein	+	LDH	306IU/L		
glucose	4+	ALP	170IU/L		
keton body	3+	ChE	253IU/L		
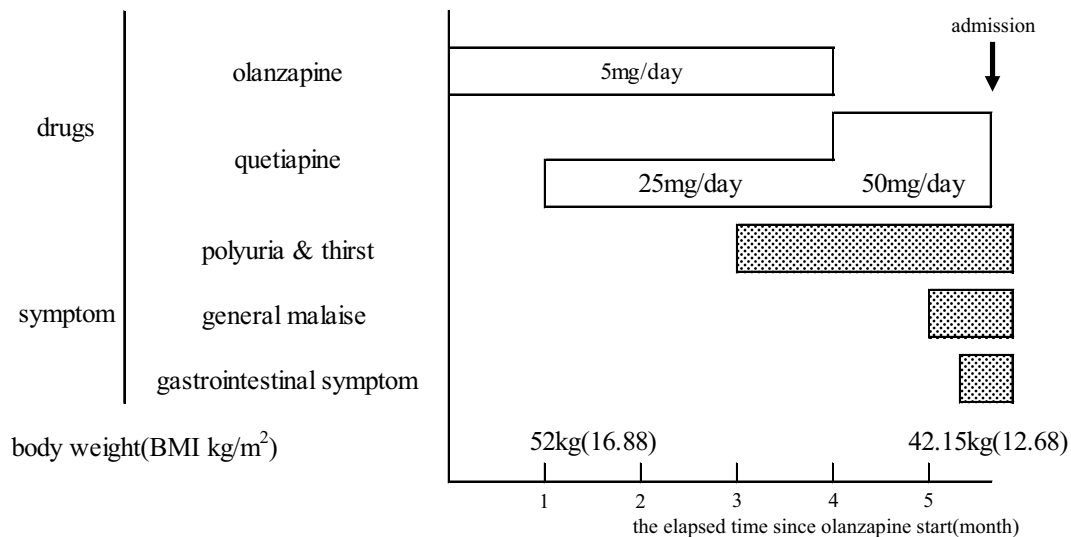
Figure 1.   Clinical course to be hospitalized from olanzapine start.

start of olanzapine treatment, he lost approximately 10 kg (52→42 kg, BMI:16.9→13.6 kg/m^2). The symptoms associated with hyperglycemia, such as polyuria, oral dryness, and compensatory polydipsia, gradually worsened. However, the treatment was continued because of the substantial improvement in the patient's psychiatric symptoms. Five months after the start of olanzapine, the subject exhibited general fatigue and presented to a local physician complaining of a loss of appetite and nausea. Blood tests revealed high blood glucose levels (540 mg/dL), and he was referred to our hospital for examination. When he arrived at our hospital, his blood glucose was 490 mg/dL, with an HbA1c of 15.5% National Glycohemoglobin Standardization Program (NGSP), positive urinary ketones (3+), and acidosis (pH 7.250) (Table 1). He was diagnosed with diabetic ketoacidosis and admitted as an emergency case, and we performed an acute metabolic correction (Fig. 1). After admission, the patient was fasted and given a continuous intravenous insulin infusion. Oral intake was restarted on the 2nd day of hospitalization (hereafter, day 2), after we corrected the hyperglycemia and the associated acute metabolic disorder. He was then put on intensive insulin therapy with Lispro and Glargine. The blood tests performed after admission showed that the patient tested negative for islet-cell antibodies (indirect immunofluorescence) (20). The patient did, however, test positive for pancreatic islet autoantibodies (with a glutamic acid decarboxylase (GAD)-antibody titer of 5.6 U/mL and an IA-2-antibody titer of 5.9 U/mL), and we noted that endogenous insulin secretion was reduced (Table 2). He met the criteria stated in the Diagnostic Criteria for Acute Type 1 Diabetes Mellitus (2012) and was therefore diagnosed with diabetes mellitus (21). After the introduction of intensive insulin therapy, the patient's blood glucose levels improved, and on day 32, the patient was discharged from the

Table 2.   Diabetes-related Laboratory Findings.

GAD antibody titer(RIA)	5.6U/mL
	reference range <1.5U/mL
IA-2 antibody titer(RIA)	5.9U/mL
	reference range <0.4U/mL
Insulin antibody binding rate(RIA)	<1.0%
	total IRI 1.7μU/mL, Free IRI 1.6μU/mL
	reference range <10%
Islet-cell antibodies(IIF)	(-)
	reference range <1.25JDF units
glucagon stimulation test (after hyperglycemia corrective)	
Fasting C-peptide	0.41ng/mL
6-min C-peptide	0.75ng/mL
HLA allele	DRB1*09(Homo)
<urine analysis>	
U-CPR	12.3μg/24h
albumin excretion rate	2.5μg/min
Ccr	155mL/min

Figure 2.   Development after hospital admission.

hospital (Fig. 2). The subject passed into a "honeymoon phase," where he required an insulin dose of <0.5 U/kg/day and his HbA1c values remained at <7% (22), from 4 months after discharge. This was maintained until the 40th month of treatment. The clinical course is shown in Fig. 3.

Discussion

SDAs are first-generation antipsychotics that are used to treat schizophrenia, and which block both dopamine D2 and serotonin 5-HT2 receptors. They also alleviate side effects such as extrapyramidal symptoms and hyperprolactinemia; they have also been observed to have effects on negative symptoms. SDAs demonstrate a similar affinity for several receptors, including the adrenergic (α1), histaminic (H1), and muscarinic receptors (1, 2), and have been shown to be effective in the treatment of schizophrenia. The APA guidelines, list SDAs as the first choice for acute treatment (3); however, these drugs are associated with the side effect of glucose intolerance (4-9). This may occasionally trigger a hyperglycemic crisis, and some fatal cases have been reported (5, 10-12). The mechanisms underlying the onset of
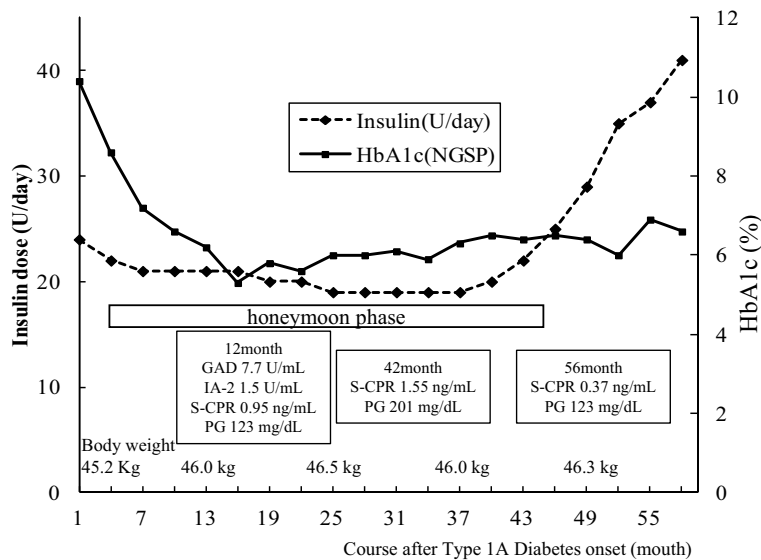
Figure 3.   Insulin dose and HbA1c after the onset of type 1A diabetes.

glucose intolerance are reported to be as follows. 1) increased insulin resistance caused by weight gain as a result of overeating due to the principal activity of SDAs, which increase the ghrelin levels by blocking the 5-HT 2C (25), D2 (26), α1 (23), and H1 receptors (23). 2) Pancreatic β-cell dysfunction (27) 3) increases the insulin resistance caused by impaired glyconeogenesis and the insulin signal transduction in L6 skeletal muscle cells (28). However, these mechanisms are associated with the onset of type 2 diabetes, and there are no reports of the onset of type 1 diabetes in relation to immunological mechanisms.

It is possible that some environmental factors (in addition to hereditary factors) contribute to the destruction of pancreatic β-cells via an immunological mechanism in type 1 diabetes. When <20-30% of the pancreatic β-cells remain, the consequent hyperglycemia leads to the onset of type 1A diabetes (13-17). However, even if >30% of the pancreatic β-cells remain, stresses such as trauma or severe infection, steroid therapy, or polydipsia can trigger a hyperglycemic state, which might accelerate the onset of type 1 diabetes (18, 19). In the present case, we found no clear causal relationship between SDA therapy and the onset of type 1A diabetes. Hypothetically, an immunological mechanism may speed up the progression of pancreatic β-cell dysfunction in pre-type 1 diabetic patients who may not necessarily present a hyperglycemic state. During this stage, the administration of SDAs and factors other than immunological mechanisms may cause marked hyperglycemia and accelerate the onset of type 1A diabetes. Thus, the administration of SDAs may be a factor that exacerbates hyperglycemia.

In the present case, the SDA-associated hyperglycemia was not caused by overeating after the start of olanzapine treatment. Thus, the possibility that the increase in the patient's insulin resistance was caused by weight gain, as a primary effect of the administration of SDAs, can be rejected. The honeymoon phase lasted for 32 months after the onset of type 1A diabetes. Although it is unlikely that olan-

zapine caused the destruction of the pancreatic β-cells, we cannot rule out the possibility that it caused reversible β-cell damage. Thus, a single, definitive cause of diabetes could not be established in the present case. Olanzapine therapy, in association with multiple factors, may have caused the patient's significant hyperglycemia, which may have precipitated or accelerated the onset of type 1A diabetes.

The authors state that they have no Conflict of Interest (COI).

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