Regular Follow-up of Olanzapine Blood Levels and Impaired Glucose Tolerance in Olanzapine-induced Diabetic Ketoacidosis: A Case Report

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ABSTRACT

A 29-year-old man was admitted to our hospital with severe nausea and hyperglycemia due to diabetic ketoacidosis (DKA). He had started receiving olanzapine (2.5 mg/day) from another hospital for clinical depression 3 months before presentation. His olanzapine plasma level on the second day (before the administration of insulin) was 1.887 ng/mL. (The therapeutic blood level is 9.3 ng/ml after 24 hours in the acute phase). By checking both the plasma level of olanzapine and the U-CPR every few days, we tried to verify impaired glucose tolerance during treatment with olanzapine. Our findings suggest that even young adults who are judged to not be at any risk of diabetes can develop DKA at low plasma concentrations of olanzapine (even in low-dose olanzapine therapy), and can recover from impaired glucose tolerance. In addition, HbA1c levels go down as insulin secretory ability improves.

INTRODUCTION

Olanzapine is widely used because of its high clinical utility, including its efficacy at ameliorating negative symptoms, resulting in improvement in quality of life. However, some side effects, such as weight gain and increased blood glucose levels, have been reported [1]. The use of olanzapine in patients therefore needs to be carefully monitored. We describe a patient who presented with diabetic ketoacidosis (DKA) 3 months after starting olanzapine treatment. There has never been a report of the quantitative tracking of the plasma concentration of olanzapine in an acute patient.

CASE PRESENTATION

A 29-year-old Japanese man was admitted to our hospital complaining of acute nausea and vomiting.

His blood glucose level was 652 mg/dL. He had been diagnosed with clinical depression 2 years before at another hospital and had been being treated for clinical depression since that time. He had been prescribed olanzapine (2.5 mg) and duloxetine (40 mg/day) 3 months before presenting at our hospital and his HbA1c level was 5.3 % that at the time of olanzapine therapy initiation. He told of being very thirsty and consuming large quantities of beverages (mostly unsweetened barley tea) 2 days before he was hospitalized. He had no other medical history and his family history was unremarkable. He had stopped smoking 1 year before and had no history of alcohol abuse. Upon admission, his height was 173 cm, body weight 70 kg, body temperature 37.2°C, pulse rate 110 beats/min, and blood pressure 144/79 mmHg. His chest was clear, his heart sounds were regular without murmurs, and his abdomen was soft and flat with no

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pain, but there was numbness in his lower limbs.

At the time of evaluation, his blood glucose was 771 mg/dL, and his urine was positive (3+) for ketones and negative for protein, and his urine glucose level was 5335 mg/day. His sodium level was 125 mEq/L, potassium 6.4 mEq/L, blood urea nitrogen 25 mg/dL, and creatinine 1.2 mg/dL. The patient's arterial blood gas values were bicarbonate 11.8 mmol/L, a partial pressure of carbon dioxide of 19 mmHg, and a pH of 7.407. The anion-gap (26.9 mmol/L) appeared to be elevated following respiratory compensation. There were no anti-insulin or GAD antibodies.

After hospitalization, we discontinued the patient's antipsychotic therapy and started him on insulin with plenty of hydration. In order to maintain a blood glucose level of 100 mg/dL, 44 human insulin units were administered over 11 hours on the first day, and the administration of an additional 37 units was required on the second day. Beginning on the third day, we changed the treatment to insulin injections four times a day to achieve glycemic control. With gas chromatography/mass spectrometry (Japan Clinical Laboratories, Inc.), we measured his plasma olanzapine levels and his daily urinary excretion of C-peptide (U-CPR/day), in parallel with glycemic control with insulin (Figure 1). His plasma olanzapine levels were 1.887 ng/mL on the first day, and decreased gradually. (The therapeutic level is 9.3 ng/ml after 24 hours in the acute phase [2].) The patient's U-CPR levels, on the other hand, were low (9.6 µg/day), and gradually increased. The patient finally recovered from his decreased insulin secretory condition. We were able to maintain his plasma glucose levels better, and start intensification therapy with Insulin Glulisine and Insulin Glargine on the 27th day. The patient was discharged on the 30th day following hospitalization (Figure 2).

We also analyzed the genetic polymorphisms of the drug-metabolizing enzymes involved in the metabolism of olanzapine (Health Sciences Research Institute East Japan Co., Ltd.). Genetic analysis of olanzapine metabolizing enzyme polymorphisms on the 185th day found that CYP1A2(*1C) and CYP1A2(*1F) were wild type, but that CYP2D6 was "*1/*1." These results suggested that this patient did not have a genotype that would indicate a loss of activity or low activity.

In addition, the patient's HOMA-IR was 11.5 on the 185th day, even though olanzapine was not present in his plasma at that point, as this was 6 months after the end of olanzapine therapy (HOMA-IR: 11.5; HOMA-β: 395%; fasting plasma C-peptide immunoreactivity: 7.58 ng/mL).
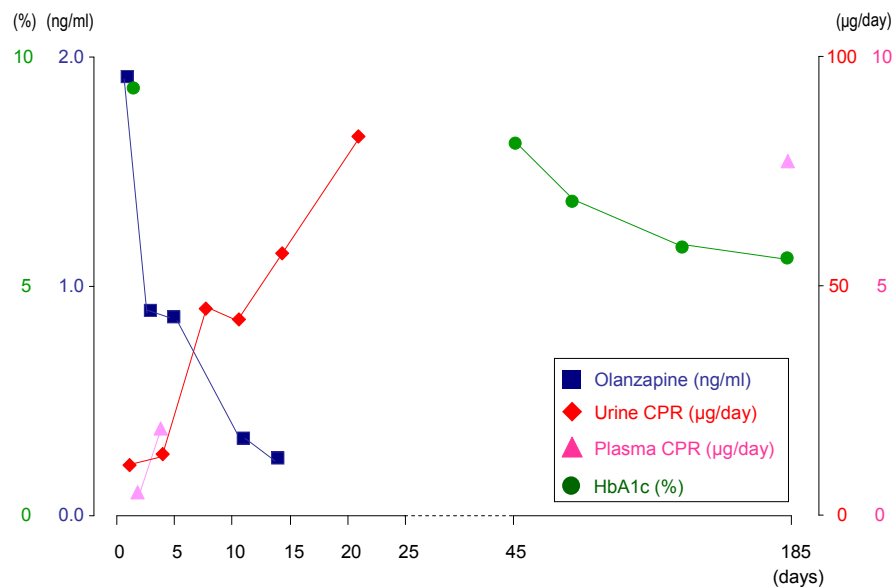
Figure 1.   Daily Plasma Olanzapine and U-CPR Levels
The quantitative values of olanzapine remained low, and decreased gradually, and the insulin secretory capacity improved as measured by U-CPR/day reversibly for about two weeks after stopping olanzapine. HbA1c levels improved gradually, and this was associated with normalization in the plasma CPR levels.
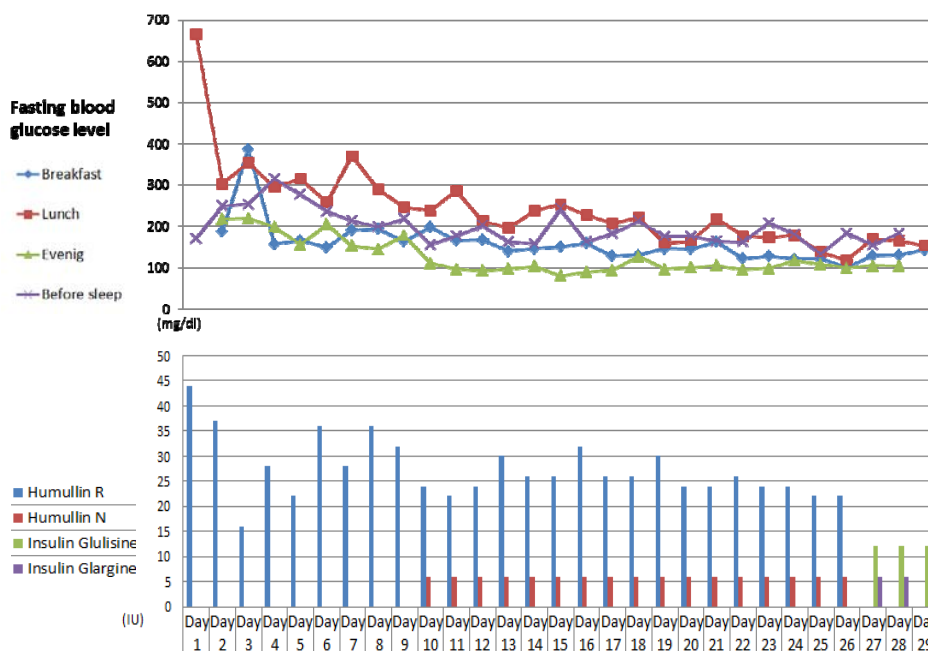
Figure 2. **Intensive Insulin Therapy and Blood Sugar Levels at Admission**
High blood sugar was remedied by intensive insulin therapy, which gradually brought the patient's blood sugar under control. The amount of insulin was reduced, and when the patient was discharged, only Insulin Glulisine and Insulin Glargine were being used, once each, in the morning. On day 72, Insulin Glulisine was stopped, and insulin therapy ended on Day 128.

DISCUSSION

Since 2000, when adverse effects were reported in a diabetic patient [3], abnormal glucose tolerance has been reported frequently. One hundred and eighty-eight out of 237 patients receiving oral olanzapine treatment were diagnosed with diabetes, and 80 of the 188 (43%) were diagnosed with DKA [4]. In addition, the incidence of DKA in olanzapine therapy was reported to be 0.8% in a report by Massachusetts General Hospital, and it is thought that infectious disease often leads to the onset of DKA in treatment with atypical antipsychotics [5]. DKA is a critical form of hyperglycemia and it can develop suddenly. It is therefore difficult to predict in many cases, and the mortality rate has been reported to range from 2% to 5%. HbA1c levels in patients who suffered from DKA at admission have been reported to be high − 13.3% ± 1.9% − according to an investigation by Henderson et al. [5]. In the present case, the patient's HbA1c level at the time of olanzapine treatment initiation was normal. The patient's olanzapine treatment was initiated after confirming that the patient did not have diabetes. When we examined the patient, his HbA1c level was 9.6%, which was low compared to the cases described above. In addition, the insulinogenic index of the patient 6 months after leaving the hospital was not low. It is interesting to note that the patient became diabetic

by taking olanzapine even though the patient's plasma levels of olanzapine were very low compared to the reports of Perry et al. [6] and Bergemann et al. [7]. Ulcickas et al. [8] reported that olanzapine exhibits a dose-dependent relationship for risk for diabetes. However, they discussed "the dose of olanzapine," but not "the plasma concentration of olanzapine." In addition, there is no background knowledge on the effects of increasing plasma olanzapine levels on enzymatic activity, such as alterations in CYP1AC and CYP2D6 levels.

In the present case, the patient's U-CPR was 9.6 µg/day at admission, and the patient's insulin secretory ability was low. Subsequently, the patient's insulin secretory ability increased in a short time and the patient's olanzapine-induced DKA exhibited reversible improvement. The result we obtained for this case, in which we regularly examined the blood level of olanzapine in an acute patient with DKA, suggest that not only low olanzapine doses, but also low olanzapine blood levels, can result in DKA. The possibility that drug interactions in combination therapy could be one reason cannot be ignored. Olanzapine is metabolized by CYP1AC and CYP2D6 and duloxetine, which is used in combination with olanzapine, is thought to also be metabolized by CYP1AC and CYP2D6, while moderately impeding CYP2D6. There has been one report that increasing the blood concentration of olanzapine interrupts the

metabolism of CYP2D6 when olanzapine is coadministered with fluoxetine, which also behaves like duloxetine [9]. Although this kind of an effect was not seen in the plasma concentration results, it is possible to conclude that it temporarily increased the blood level of olanzapine resulting from "low-dose" olanzapine. Seaburg et al. has reported that "Olanzapine has been associated with insulin resistance and new-onset diabetes mellitus" [10]. Therefore, patients should be carefully monitored for high HOMA-IR levels even when olanzapine is not present in plasma, (as in this case, when the HOMA-IR was high even 6 months after treatment with olanzapine).

Cross-checking the report from Seaburg et al. against our case, we can conclude that patients can develop DKA when they exhibit insulin resistance, even if the plasma concentration of olanzapine is low. We can also conclude that there is no relationship between the presence of insulin resistance and the plasma concentration of olanzapine, and that improvement in olanzapine-induced DKA is achieved as the U-CPR increases, but does not depend on the plasma concentration of olanzapine. It is thought that future research is needed into the causes of low-dose-olanzapine-induced DKA and the adverse effects of drug interactions in combination therapy with drugs such as duloxetine.

CONCLUSIONS

Olanzapine-induced DKA is a reversible clinical condition that improves with the recovery of insulin secretion capacity. Although olanzapine-induced insulin hyposecretion is reversible, caution is required when using even low doses of olanzapine.

ACKNOWLEDGMENTS

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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