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Diabetic Ketoacidosis and Diabetes Mellitus Caused by Trazodone: A Rare Case Report

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ABSTRACT

We describe a 28-year-old male with a history of schizophrenia who developed diabetic ketoacidosis and diabetes mellitus within 3 months after starting on trazodone to replace aripiprazole, and then the hyperglycemia and hemoglobin A1c level regained normal levels within 3 months after trazodone was stopped. To our knowledge, this is the first ever report on trazodone causing hyperglycemia. We therefore suggest checking blood glucose level before and after prescribing trazodone. Trazodone should be discontinued when hyperglycemia is detected, and alternative medication than trazodone should be considered for patients with diabetic history.

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Case Description

A 28-year-old Asian male based in Guam with a history of schizophrenia that was diagnosed three years ago when he was placed on aripiprazole by his psychiatrist. He was maintained on aripiprazole until 3 months ago when he was taken to the Philippines (PI) for a second opinion, where the aripiprazole was changed to trazodone at 150 mg daily. The blood work performed one week before the medication change revealed a Hemoglobin A1c (HbA1c) of 5.2% and an unremarkable basic metabolic profile. He was not on any other medications before and after the medication change. Three months later, he presented to our emergency room with generalized weakness, poor appetite, fatigue, and nausea for one week. Review of systems were positive for polyuria and polydipsia but negative for abdominal pain, vomiting, diarrhea, cough, dysuria, rash, or fever. He was initially normotensive (112-134/56-77 mmHg). Tachycardia (102-120 bpm) and tachypnea (26 respirations per minute) were also appreciated, along with normal oxygen saturation (SpO2 95-99% on room air) and mentation. Of note, his body mass-index (BMI) was 24.3. Physical examination demonstrated extremely dry oral mucosa and vague tenderness over the periumbilical abdomen with no rebounding tenderness. Bowel sound was active. Initial venous blood gas showed pH of 7,1, pCO2 of 28 mmHg, pO2 of 174 mmHg, HCO3- of 7.3 mmol/L, and lactate of 2.54 mmol/L. Basic metabolic profile showed blood glucose of 693 mg/dL, anion gap of 26 mEq/L, creatinine of 1.3 mg/dL, and blood urea nitrogen of 22 mg/dL. Initial serum sodium, potassium, chloride, calcium, and magnesium levels were normal. Urinalysis was negative for pyuria or bacteriuria. Chest X-ray was negative for evidence of pneumonia. CT abdomen and pelvis showed no suspicious infection focus or other abnormalities. Nonetheless, HbA1c was now measured at 11.3%. Serum and urine were positive for ketones. Electrocardiogram showed normal QTc interval at 412 ms. Under a working diagnosis of diabetic ketoacidosis (DKA), the patient was admitted to the intensive care unit (ICU).

Insulin drip and concurrent lactate ringer hydration were started. Eight hours later, his anion gap was reduced to 12 mEq/L, and then insulin drip was replaced by insulin glargine. Potassium and magnesium were also repleted during the insulin infusion. Patient was stabilized and transferred out of ICU on the next day. He was subsequently visited by his previous psychiatrist who restarted him on aripiprazole and trazodone was stopped. Three months later, his HbA1c decreased to 5.6%. It was then confirmed that the patient did not take any insulin in these three months due to fear of pain upon injection, nor did he take any oral medications for diabetes mellitus (DM).

Discussion

DKA is one of the most common reasons for ICU admission [1]. More than 90% of the DM-related admissions are DKA [2]. The incidence of DKA has increased over the years, in parallel with the rising prevalence of DM [3]. For a long time, it was believed that only type 1 DM can cause DKA, but we now have observed more DKA cases from type 2 DM. DKA is often precipitated by infection, stress, surgery, trauma, or medication noncompliance [4]. The presentation includes non-specific symptoms like fatigue and weakness, gastrointestinal symptoms such as nausea, vomiting, and abdominal pain, and diabetic symptoms including polyuria, polydipsia, and polyphagia. The patients almost universally show signs of profound dehydration, and some may even be in

hypovolemic shock. Diffuse tenderness over the abdomen is also common. The laboratory findings typically include remarkable hyperglycemia (mostly > 500 mg/dL), yet some patients are euglycemic or only slightly hyperglycemic [5]. Metabolic acidosis is usually present but the venous pH level rarely dips below 7. Hypovolemic hyponatremia from dehydration or pseudo hyponatremia secondary to aggravated hyperglycemia may also take place, as well as acute kidney injury from prerenal azotemia. The diagnostic approach for DKA begins with the identification of an increased serum anion gap, followed by checking for the presence of ketones including beta-hydroxybutyrate or acetoacetic acid in blood or urine while the other causes for anion gap metabolic acidosis including lactate acidosis from either shock, ischemic bowel, liver failure, or post-seizure, and organic acids accumulation in the blood from renal failure will have to be excluded. The DKA treatment would prioritize copious crystalloid fluid replacement as most patients are volume depleted from prolonged glucosuria stemmed from prolonged hyperglycemia, followed by insulin infusion until the serum anion gap is normalized, and then the patient can be transitioned to scheduled insulin or oral hypoglycemic agents. During the insulin infusion, serum potassium and magnesium are shifted intracellularly so both need to be replaced proactively. Bicarbonate infusion is controversial for patients with metabolic acidosis, as ketoacidosis usually improves quickly with insulin infusion alone [6].

We hereby present a young man who developed DKA three months into his trazodone course. The HbA1c at ICU admission confirmed that he was severely diabetic, whereas his HbA1c was normal right before starting on trazodone. Given the patient was only 28 years old with normal BMI and waist conference, and he had no personal or family history of DM, he was very unlikely to develop type 2 DM within such a short period of time. Maturity-onset diabetes of the young (MODY) and juvenile type of diabetes (Type 1 DM) were not plausible diagnoses as his HbA1c would not return to normal without diabetic treatment if he had either condition. Moreover, he was not on any other medications or folk therapies that could raise his glycemia, and his diet had not changed from baseline. As HbA1c reflects the overall blood glucose level for the past 3 months, the only explanation left for his increment in HbA1c was trazodone. However, trazodone has generally been considered safe for diabetic patients and it is the second line therapy for diabetic neuropathy [7]. To our knowledge, this is the first case report depicting trazodone as a potential cause for DM, for blood glucose level is generally unchanged with trazodone. One literature reported that trazodone was associated with hypoglycemia by attenuating the metabolism of pioglitazone when taken together, causing blood glucose level to decrease [8]. In another research, the mean HbA1c level was shown lower among the diabetic patients receiving trazodone compared to other first-line antidepressants [9]. For now, there has been no literature reporting that trazodone would raise blood glucose level, and there has been no case report associating trazodone with DKA as well. In our case, trazodone probably first caused substantial DM, and then DKA in turn occurred from the uncontrolled DM, as the infection workup was negative and there was no evidence that the patient was under acute psychological stress, which is a common trigger for DKA in psychiatric patients [10]. Some argue that his hyperglycemia might be due to taking aripiprazole, for hyperglycemia is not an uncommon side effect for the antipsychotic, whereas the DKA from aripiprazole usually emerges within 2-4 weeks, which is inconsistent with the clinical timeline of our case, not to mention the restart on aripiprazole actually saw his HbA1c improved paradoxically [11].

Trazodone is a serotonin-2 receptor antagonist, while it also antagonizes α1-adrenoceptors. The double blockage brings about significant sedative effects, so it is often prescribed off-label for insomnia. An increase in slow-wave phase on polysomnogram and total sleep time on patients taking trazodone is often observed [12]. With a relatively safe profile and inexpensive cost, trazodone was the 18th most commonly prescribed medicine in the United States in 2022 to mainly treat insomnia [13]. It is also prescribed for depression as a second-line antidepressant as its metabolite, m-chlorophenylpiperazine, is a serotonin receptor agonist. In our case, trazodone was likely prescribed to control the negative symptoms of schizophrenia [14]. Since trazodone potentially causes hyperglycemia via unclear mechanisms that life-threatening hyperglycemic complications such as DKA can emerge, checking blood glucose level before and after the patient starts on trazodone may be warranted, and trazodone probably should not be given to patients with baseline hyperglycemia. Trazodone discontinuation is also recommended if hyperglycemia is detected after trazodone is started. Meanwhile, hyperglycemia caused by trazodone may resolve spontaneously within 3 months after its discontinuation, hence the patient may not need to continue diabetic treatment after the HbA1c returns to normal range. In addition, the dose taken by this patient was higher than the dose commonly used for insomnia, so it is unclear whether DM and DKA occurrence was associated with a higher dosage of trazodone, which may help explain why trazodone has never been reported for hyperglycemia, given most people take it merely for insomnia at 25 to 50 mg at bedtime.

Further studies to explore if hyperglycemia is a consistent side effect among the patients taking higher dosage of trazodone for depression or schizophrenia is probably of merit. As we do not know the specific risk factors, for example, certain genetic polymorphism for triggering DKA and DM by trazodone, clinicians should be mindful of the hyperglycemic effects when prescribing trazodone. For the patients who already have DM history, trazodone prescription should probably be refrained for the glycemic control may worsen afterwards.

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