Hyperosmolar Nonketotic State Associated with Quetiapine
Ketiapin Kullanımına Bağlı Hiperglisemik Hiperosmolar Koma

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Abstract
A 67-year-old man was admitted to our hospital because of decreased oral intake and confusion. He had a 2-year history of diabetes mellitus and he had a good glycaemic control with oral antidiabetic drugs (latest HbA1C:7.2%). Quetiapine was initiated 15 days ago in a psychiatric clinic because of depression. The patient was taken to the intensive care unit with the diagnosis of hyperosmolar nonketotic state and acute renal failure. All the medications were discontinued; intravenous hydration and insulin infusion were started. The relationship between second-generation antipsychotics (SGAs) and hyperglycemia is a topic of interest and insulin resistance is commonly accepted as the mechanism for hyperglycemia. Patients receiving SGAs should be followed more closely for metabolic disorders. Turk Jem 2014; 18: 140-142
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Özet
Anahtar kelimeler: Ketiapin, hiperglisemik hiperosmolar durum, tip 2 DM

Introduction
Second-generation antipsychotics (SGAs) include clozapine, risperidone, olanzapine, and quetiapine. They provide a great benefit to many patients with different psychiatric disorders, especially to patients with schizophrenia. The adverse effects of these drugs are: increased risk of obesity, diabetes, and metabolic syndrome. They may also directly increase insulin resistance, the risk of developing diabetes, dyslipidemia and hypertension. We report a case of a sixty-seven-year-old man who developed hyperosmolar nonketotic state and acute renal failure whilst receiving quetiapine for a depressive episode.

Case Report
A 67-year-old man with the diagnosis of type 2 diabetes mellitus (DM) for 2 years was admitted to the emergency department (ED) because of decreased oral intake and confusion. He was on oral antidiabetic drug therapy (metformin 2000 mg/day, gliclazide 30 mg/day). He had a good glycaemic control and the latest HbA1C level was 7.2% which was measured 2.5 months ago. Dementia and severe depressive episode with psychotic symptoms were diagnosed 4 months ago. Quetiapine 200 mg/day was started alone 15 days ago in the psychiatric clinic.

His symptoms had started 3 days ago and then gradually increased until the day of admission. On physical examination, body temperature was 36.7 °C, heart rate was 111 beats/min, arterial blood pressure was 130/80 mmHg. The general condition was moderate and he was somnolent. There was response to painful stimuli. Pupillary light reflexes were intact. Glasgow coma scale score on admission was 14. Tongue and mucous membranes were dry, turgor tone was markedly reduced. Cardiovascular examination revealed tachycardia. Remaining systemic examination was normal. Initial laboratory tests in the ED included: plasma glucose: 776 mg/dL (70-105), urea: 382 mg/dL (15-44), creatinine: 4.2 mg/dL (0.57-1.11), sodium: 164 mEq/L (136-145), amylase: 130 U/L (25-125), lipase: 81 U/L (8-78), total bilirubin: 1.3 mg/dL (0.2-1.2), and direct bilirubin: 0.5 mg/dL (0-0.5). The other biochemical parameters were normal. Hemoglobin
was 16.6 gm/dl (12.1-17.2), hematocrit was 51% (36.1-50.3%), and WBC was 20.2x10^3/μL (3.5-10). Sedimentation rate was 91.9 mm/h, C-reactive protein was 46.9 mg/L, arterial blood pH was 7.48 (7.35-7.45), pCO₂ was 26 mmHg (35-45), pO₂ was 57.2 mmHg (75-100), bicarbonate was 21 mEq/L (21-27), urine glucose was 300 mg/dL and urine ketones and leukocytes were negative. The calculated serum osmolality was 400 mOsm/kg (285-295). Initial electrocardiogram revealed first degree AV block and sinus tachycardia. Posteroanterior chest radiograph was evident with enlarged aortic knob and normal lung parenchyma. The patient was taken to the intensive care unit and treatment was started immediately with the diagnosis of type 2 DM, hyperosmolar nonketotic state and acute renal failure. Acute renal failure and hypernatremia were considered to be caused by dehydration. Adequate intravenous (IV) hydration therapy was initiated. Quetiapine and oral antidiabetics were discontinued and insulin infusion was started. Although there was no precise focus of infection, a broad spectrum antibiotic, IV ceftriaxone 2x1 g/day, was started. Patient's general condition and laboratory findings improved rapidly. The laboratory tests while he was being discharged from a 10-day hospital stay revealed that glucose was 137 mg/dL (70-105), sodium was 139 mEq/L, potassium was 3.5 mEq/L, urea was 22 mg/dL, and creatinine was 1.0 mg/dL. The patient's current oral antidiabetic therapy was resumed at discharge but quetiapine was discontinued.

**Discussion**

In this paper, we report a patient with exacerbation of preexisting DM due to quetiapine which is a member of SGAs. The underlying mechanism of SGA-related glucose-lipid metabolic disorders is not fully understood. SGAs may lead to weight gain, but they may also directly increase insulin resistance, the risk of developing diabetes, dyslipidemia, and hypertension. There is extensive evidence that SGAs, particularly clozapine and olanzapine, and to a lesser extent risperidone and quetiapine, are associated with drug-induced weight gain and emphasizing the role of insulin resistance [1,2]. Some authors reported that diabetes may develop independently of weight gain, rather rapidly and possibly progressing to ketoacidosis, thus, arguing for a severe impairment of insulin secretion. Recent studies have suggested a possible impact of SGAs on endocrine regulation, especially on adipocytokines. Sugai et al. have found that patients receiving SGAs had significantly higher leptin levels compared to control subjects. The plasma concentration of adiponectin, total cholesterol and high-density lipoprotein cholesterol in SGA subjects were significantly lower than those in controls [3].

In the literature, there are reports describing acute hyperglycemia due to these kinds of drugs. Jin et al. analyzed 45 published cases of new-onset DM or diabetic ketoacidosis (DKA) that occurred after initiation of atypical antipsychotic treatment. Of the 45 patients, 20 had received clozapine, 19 olanzapine, 3 quetiapine and 3 risperidone. Forty-two percent of these patients presented with DKA, and fifty percent of them manifested no weight gain at the time of presentation with DM or DKA, although 84% were overweight before antipsychotic therapy [4]. Koller et al. identified 46 reports of quetiapine-associated hyperglycemia or diabetes. Of the reports of quetiapine-associated hyperglycemia, 34 patients had newly diagnosed hyperglycemia, 8 had exacerbation of preexisting DM, and 4 could not be classified. Most cases appeared within 6 months of quetiapine initiation. The severity of cases ranged from mild glucose intolerance to DKA or hyperosmolar coma. There were 21 cases of ketoacidosis or ketosis. There were 11 deaths (5). Several reports supported that severe hyperglycemia and pancreatitis may be associated with SGAs [6]. They may lead to hyperglycemia or DKA. The mechanism of hyperglycemia is not clear. It may be related to weight gain as a result of abnormal eating behavior. Rashid et al. reported a patient who developed pancreatitis and life-threatening DKA while receiving ziprasidone 80 mg orally, twice daily, and quetiapine 200 mg orally, at bedtime for nine months [7]. A 27-year-old man who was treated with quetiapine for anxiety disorder and developed hyperglycemia-induced acute pancreatitis and DKA has been reported by Madsen KR from Denmark [8]. The patient was otherwise physically healthy with no family history of hyperlipidemia. Despite aggressive intensive therapy, he died because of multiorgan failure within 36 hours from initial presentation. In the literature, acute hyperglycemia due to SGAs is mostly reported to be associated with ketoacidosis. In our case, the patient presented with hyperglycemic hyperosmolar state. DKA and hyperglycemic hyperosmolar state are the two endpoints of the spectrum. This may be due to the metabolic status of the patients and/or quetiapine may have led to this situation. In our case, the patient with a regulated DM presented with hyperglycemic hyperosmolar state that may be associated with quetiapine 200 mg/day which was initiated 15 days ago. In treatment-resistant depression, the initial quetiapine dose is 5 mg/day, and the dose is titrated up to a maximum of 150, 300, or 600 mg/day, with a mean dose of 182 mg/day and 150 or 300 mg/day (9,10,11). Our patient was receiving the drug in the appropriate dose range.

As a result, plasma glucose, weight and lipid profiles should be carefully monitored by the clinicians in patient receiving SGAs. In the same manner, the guidelines issued in 2004 by the American Diabetes Association and the American Psychiatric Association recommended baseline screening and ongoing monitoring of plasma glucose and lipid levels in patients receiving SGAs [12]. Appropriate patient education should include the signs and symptoms of acute metabolic disorders.

**Conflicts of Interest**

There are no conflicts of interest.

**References**


