Clozapine associated diabetic acidosis

**Kalliopi Kotsa, Evangelos Potosidis, Vasiliki Lygoura,
Charalampos Mandros, Panagiotis Fanourgiakis**

ABSTRACT

Abstract is not required for Letter to Editor

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LETTER TO EDITOR

OPEN ACCESS

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Kalliopi Kotsa, Evangelos Potolidis, Vasiliki Lygoura, Charalampos Mandros, Panagiotis Fanourgiakis

To the Editor,

Sir,

Clozapine is a second generation antipsychotic drug used to treat resistant schizophrenia and suicidal behavior. It binds to D₁, D₂, D₃ receptors, has high affinity to D₄ receptors, but binds transiently to D₂ receptors. Clozapine interacts at histamine H₁, acetylcholine muscarinic M₁, serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT₆ and 5-HT₇ receptors and at alpha-1-adrenoreceptors [1]. Its bioavailability is 60-70% and the half life is 14 hours [2]. The drug is metabolized by the cytochrome system in the liver (P₄₅₀). Tobacco smokers require higher doses than non-smokers, because tobacco induces cytochrome CYP_{1A2}. Norclozapine is the major metabolite of clozapine and has not any therapeutic activity [3]. Patients who require treatment with clozapine should receive routine weekly monitoring in order to avoid adverse events such as agranulocytosis, myocarditis, pulmonary embolism, and diabetes mellitus with ketoacidosis development [4–7]. The white blood count should be checked weekly during the first six month of therapy. A WBC >3500/mm³ and an absolute neutrophil count >2000/mm³ are required

for continuing therapy. Cardiovascular system should be closely monitored during the first month of treatment due to rare cases of clozapine associated myocarditis and heart failure. We present a case of a 24-year-old obese male who developed hyperglycemia and severe diabetes ketoacidosis while he was receiving therapy with clozapine for schizophrenia and suicidal behavior. The patient was brought to hospital due to abdominal discomfort, polydipsia, and polyuria. He suffered from schizophrenia with suicidal behavior and received clozapine 300 mg daily during the last month. The patient was obese with a body mass index of 42 kg/m². His temperature was 36.8°C, respiratory rate was 30/min, blood pressure was 100/55 mmHg and pulse note was 125 beats/min. He appeared ill, pale, and dehydrated. The lungs were clear, heart and abdomen were normal. Spleen and liver were not felt. He had cool extremities, confusion, and weakness. Tendon reflexes and cranial nerves were normal. Blood examinations revealed glucose 400 mg/dL, urea 130 mg/dL, creatinine 2.3 mg/dL, Hematocrit 39%, white blood cell count 9230/mm³ and ANC 5070/mm³, potassium 3.0 mmol/L and sodium 129 mmol/L. Arterial blood was drawn and revealed metabolic acidosis with increased anion gap. The pH was 6.9, pO₂ 98 mmHg, pCO₂ 19 mmHg, HCO₃⁻ 10 mmol/L and lactate 0.9 mmol/L. He was admitted to the Internal Medicine Department. X-ray and electrocardiogram were normal. Blood and urine were cultured. Saline, potassium, and insulin (10 units/hour) were given intravenous. Within several hours after admission glucose fell to 200 mg/dL and the pH increased to 7.28. On the second day of admission, the pH was 7.38 and the patient was able to eat. He received glargine at bedtime and glulisine before meals. Blood and urine cultures were negative. Glycosylated hemoglobin (HbA_{1c}) was 9.5%, which reveals that the patient had unbeknown diabetes and the metabolic deterioration have been aggravated by the clozapine therapy. On the third day of admission, blood glucose, electrolytes, thyroid function, and arterial gases were normal. Ultrasonography of abdomen was normal, and on the fourth day, he was discharged. Clozapine is used to treat schizophrenia and suicidal behavior. A dose

Kalliopi Kotsa¹, Evangelos Potolidis², Vasiliki Lygoura³, Charalampos Mandros⁴, Panagiotis Fanourgiakis⁴

Affiliations: ¹PhD, MD, Lecturer in Endocrinology, Dept of Endocrinology, AHEPA, University Hospital, Aristotle University of Thessaloniki, GREECE; ²MD, General Hospital of Volos, Greece, Department of Internal Medicine; ³MD, Department of Internal Medicine, General Hospital of Volos, GREECE; ⁴PhD, MD, Department of Internal Medicine, General Hospital of Volos, GREECE.

Corresponding Author: Evangelos Potolidis, MD, Internist, Department of Internal Medicine, General Hospital, of Volos, Greece, Dafnis 1,38222 Volos, GREECE; Tel/Fax: +00302421076680, Mobile: 6974874698; Email: potol13@gmail.com

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of 300–600 mg daily is required for treatment. Clozapine plasma level should be in the range of 250–350 ng/mL. Prior to treatment the patient should be carefully evaluated.

The white blood cell count must be checked weekly for the first six months if the patients are receiving clozapine, every other week for the second six months, every month after one year and for one month after clozapine is stopped, according to the current guidelines. Henderson et al. were able to show that of 96 patients with chronic schizophrenia treated with clozapine and followed for up to 10 years, 34% developed diabetes [7]. Physicians need to be aware of clozapine induced diabetic ketoacidosis. Patients should have pre-treatment assessment with WBC, ANC, glucose, HbA1c, lipids, clinical examination, and ECG in order to avoid hazardous adverse effects.

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The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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ABOUT THE AUTHOR

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Evangelos Potolidis is Consultant in Internal Medicine at Department of Internal Medicine, General Hospital of Volos, Greece. His area of interest include Diabetology.

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