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Aggravation of Acute Adrenal Crisis Due to Varenicline in a Patient with Adrenal Insufficiency

Variniklinle İndüklenen Akut Adrenal Kriz: Olgu Sunumu

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Abstract

We present a male patient with the diagnosis of primary adrenal insufficiency. He had acute adrenal crisis while receiving varenicline treatment for smoking cessation. The patient was examined carefully for the potential cause of adrenal crisis. His medical history was unremarkable except for varenicline use that started one week ago. We report here the first case of a patient who developed acute adrenal crisis under varenicline treatment.
Keywords: Varenicline, adrenal, insufficiency

Öz

Biz bu çalışmada primer adrenal yetmezliği olan erkek olguyu sunduk. Sigara bırakmak için vareniklin kullanılan hastamızda adrenal kriz gelişti. Hasta muhtemel adrenal kriz nedenleri ile ilgili dikkatlice tetkik edildi. Tek farklılık bir hafta önce vareniklin tedavisi başlamasıydı. Vareniklin tedavisi altında akut adrenal kriz gelişen ilk olgu sunumunu rapor ettik.
Anaktar kelimeler: Vareniklin, adrenal, yetersizlik

Introduction

Smoking is a modifiable risk factor for premature death and all-cause mortality (1). It is one of the leading causes of mortality in the world. As a result, many therapies have been used for smoking cessation. Varenicline, an orally administered tablet which is an approved agent for tobacco cessation, is a specific partial agonist of the α4β2 nicotinic acetylcholine receptor that release dopamine in the meso-limbic area of the brain and alleviate withdrawal symptoms (2). After quitting, symptoms usually start within a few hours of the last cigarette and peak about 2 to 3 days later. Withdrawal symptoms can include dizziness, depression, feelings of frustration and anger, anxiety, irritability, sleep disturbances, headaches and increased appetite.

Varenicline increases the success of long-term smoking cessation, compared with pharmacologically unassisted quit attempts (3). The reported side effects of varenicline include nausea, vomiting, neuropsychiatric and sleep disturbances.

Primary adrenal insufficiency (Addison's disease) is a life-threatening event, resulting from destruction or dysfunction of the adrenal cortex. It is associated with significant morbidity and mortality, but after diagnosis, it can be easily treated (4). Acute adrenal insufficiency, termed an adrenal crisis or Addisonian crisis, is a medical emergency manifesting as hypotension and acute circulatory failure. Anorexia, nausea, vomiting, diarrhea, and abdominal pain may occur (5). We present the case of a patient with the diagnosis of adrenal insufficiency in whom varenicline treatment led to acute adrenal crisis.

Case Report

The patient was a 24-year-old man who had the diagnosis of adrenal insufficiency for 20 years and was being treated with 30 mg/dL of oral hydrocortisone and 0.2 mcg/dL oral fludrocortisone. He was taking his medication orderly and had no aggravation for a long time. He had started smoking one year ago and was receiving varenicline treatment for a week. The patient was admitted to our emergency department with the complaints of fatigue and shortness of breath for the last 3 days. On physical examination, his temperature was 36 °C, blood pressure was 90/60 mmHg and heart rate was 96 beats/minute. The patient's initial laboratory data at the admission were as follows: Blood urea nitrogen: 41 mg/dL, creatinine: 1.12 mg/dL, sodium: 122

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mEq/L, potassium: 7.1 mEq/L, white blood cells: 8.8×10^9/L, and C-reactive protein: 6.12 mg/L.

The patient was referred to our intensive care unit because of hypotension, hyponatremia and hyperpotassemia. Physical symptoms and laboratory findings were consistent with adrenal crisis. Varenicline treatment was terminated and intravenous methylprednisolone 2x40 mg and hydration was initiated. The sodium and potassium levels had returned to the normal limits after the treatment. On the follow-up, the patient ameliorated and the methylprednisolone dosage was decreased. The patient was discharged on maintenance therapy.

Discussion

Primary adrenal insufficiency is caused by impaired adrenal function. It is characterized with low cortisol production and high plasma adrenocorticotropic hormone (ACTH) concentration. Two major adrenal steroids that play important role in the syndromes of adrenal insufficiency are cortisol and aldosterone. The causes of primary adrenal insufficiency include idiopathic causes (65%), tuberculosis (20%), other causes (15%), fungi, adrenal hemorrhage, metastasis, sarcoidosis, amyloidosis, adrenoleukodystrophy, adrenomyeloneuropathy, acquired immunodeficiency syndrome, congenital adrenal hyperplasia, congenital adrenal hypoplasia, and congenital unresponsiveness to ACTH (6). Our patient had idiopathic adrenal insufficiency.

Acute adrenal crisis is a medical emergency manifesting as hypotension and acute circulatory failure. Anorexia, nausea, vomiting, diarrhea and, sometimes, abdominal pain may be present. Fever and hypoglycemia may occur. Progressive hyperkalemia and shock should alert the clinician for the diagnosis.

In laboratory findings, hyponatremia (90%) and hyperkalemia (60%) are usually present. Basal plasma cortisol and urinary free cortisol levels are often in low-normal range. In ACTH stimulation test, the response is inadequate (plasma cortisol <20 µg/dL, 30 minutes after ACTH administration).

Treatment of acute adrenal crisis is hydrocortisone and saline infusion. Hydrocortisone should be given at a dose of 100 mg every 4-6 hours. In patients with shock, 1 L saline infusion should be given in the first hour. Long-term replacement therapy includes oral hydrocortisone (usually 15-25 mg/dL in divided doses) and mineralocorticoid (in form of fludrocortisone 0.05-0.2 mg/dL). Patients on glucocorticoid replacement therapy should be advised to double their daily dose in the event of intercurrent febrile illness, accident, or mental stress. Premedication may be given before minor and major surgery. Pregnancy may necessitate an increased dose of hydrocortisone (5).

Hahner et al. (7) evaluated 526 patients with chronic adrenal insufficiency for adrenal crisis. Precipitating causes were gastrointestinal infection (21.8%), other infectious diseases/fever (17.3%), surgery (15.5%), unknown (12.7%), strenuous physical activity (7.3%), cessation of glucocorticoid substitution by patient (6.4%), neglected glucocorticoid intake (3.6%), psychic distress (3.6%) accident (2.7%) cessation of glucocorticoid substitution by attending physician (3.6%), and other reasons.

Adrenostatic drugs like etomidate or ketoconazole or drugs that accelerate cortisol metabolism like barbiturates, rifampicin or mitotane may trigger adrenal crisis (7). The mechanism of interaction between glucocorticoids and rifampicin is based on the ability of rifampicin to induce the cytochrome (CYP) 3A4, which metabolizes glucocorticoids in the liver (8).

Our patient was diagnosed with adrenal insufficiency 20 years ago. During follow-up, he had two adrenal crises because of infection. He had being treated with 30 mg/dL of oral hydrocortisone and 0.2 mcg/dL oral fludrocortisone regularly as replacement therapy. In admission, his body temperature was 36 °C. Physical examination and laboratory results showed no evidence of infection. In his history, he had no emotional stress and his physical activity was as per usual. Recently the only change was varenicline treatment that started one week before at a dose of 0.5 mg/day for the first 3 days and 1 mg/day for the consequent 4 days. His symptoms developed before scheduled "quit date" and he was already smoking. On his inquiry, he had no evident stress about smoking cessation. He was also examined for the withdrawal symptoms but he did not define any symptom. Approximately 90% of varenicline is excreted in the urine unchanged (9). Varenicline does not undergo significant metabolism and is not metabolized by hepatic microsomal CYP P450 enzymes. In vitro, varenicline does not inhibit nor induce the activity of the major CYP enzymes (10). The accumulated data do not give a hint for the potential mechanism generating an interrelation between varenicline and glucocorticoid metabolism. One of the adrenal crises may be drug interaction, but the mechanism is unclear according to the current data.

Varenicline may apply potential depressogenic effects on a biological level. The literature implicates adapted hypothalamic, pituitary, adrenal (HPA) axis activity and flexibility in depression (11). Furthermore, HPA axis alterations, e.g., Cushing's disease or corticosteroid treatment, may induce depression (12). In addition, HPA axis alterations predict depression development or recurrence (13,14). Therefore, the HPA axis has been used as a measure of risk of depression development (15). It may be that varenicline exerts its suggested depressogenic effects through other less well-known biological pathways. This would fit with associations of varenicline with depression and suicide reported in post-marketing surveillance studies (16). However, some studies have reported opposite results. Mocking et al. (17) demonstrated that 7 days varenicline treatment in healthy non-smoking subjects had no influence on the cortisol awakening response, thereby, not suggestive of depressogenic effects on the HPA axis.

To our knowledge, there is no report describing clinically evident acute adrenal insufficiency during varenicline therapy. We report here the first case of a patient with chronic adrenal insufficiency who developed acute adrenal crisis under varenicline treatment. Physicians should be aware of this rare but potentially fatal complication when considering varenicline therapy especially in patients with chronic adrenal insufficiency. The possible mechanism is unclear. We need more data to seal the relationship between varenicline and adrenal insufficiency. However, to

our opinion, a detailed physical examination and necessary laboratory tests may be performed before starting varenicline treatment in patients with chronic adrenal insufficiency and the patients should be followed up more carefully for adrenal crisis.

Ethics

Informed Consent: Informed consent was obtained from our patients for being included in this case report.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Elif Turan, Bülent Savut, Mustafa Kulaksızoğlu, Feridun Karakurt, Concept: Elif Turan, Yaşar Turan, Bülent Savut, Mustafa Kulaksızoğlu, Feridun Karakurt, Design: Elif Turan, Yaşar Turan, Bülent Savut, Mustafa Kulaksızoğlu, Feridun Karakurt, Data Collection or Processing: Elif Turan, Yaşar Turan, Bülent Savut, Analysis or Interpretation: Elif Turan, Literature Search: Elif Turan, Writing: Elif Turan, Yaşar Turan.
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