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Olgu Sunumu/Case Report

Possible hiccup-inducing mechanism of aripiprazole: a case report

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Abstract

Hiccup is an involuntary, intermittent, spasmodic contraction of the diaphragm and inspiratory muscles resulting in sudden inspiration and ending with abrupt closure of the glottis, followed by a peculiar sound. The underlying mechanism of hiccups is poorly understood, but the use of therapeutic drugs constitutes one of the important causes of hiccups. The possible hiccup-inducing mechanism of aripiprazole is discussed in this case which was developed by starting aripiprazole treatment in a patient with a depressive disorder.

Key words: Antipsychotic; Aripiprazole; Hiccup

Aripiprazolün Olası Hıçkırığa Neden Olma Mekanizması: Bir Olgu Sunumu

Özet

Hıçkırık, diyafragma ve inspiratuar kasların, ani bir inspirasyona neden olup, glottisin kapanmasıyla son bulan, tuhaf bir ses çıkmasına neden olan istemsiz, aralıklı ve spazmodik kasılmasıdır. Hıçkırığın altında yatan mekanizma az anlaşılmıştır, ancak terapötik ilaçların kullanımı hıçkırıkların önemli nedenlerinden birini oluşturmaktadır. Biz bu olgu sunumunda, major depresif bozukluk nedeniyle aripiprazole tedavisi başlanan bir hastada ortaya çıkan hıçkırığın olası mekanizmalarını tartıştık.

Anahtar kelimeler: Antipsikotik; Aripiprazol, Hıçkırık

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Introduction

Hiccup is an involuntary, intermittent, spasmodic contraction of the diaphragm and inspiratory muscles resulting in sudden inspiration and ending with abrupt closure of the glottis, followed by a peculiar sound. Hiccups lasting longer than 48 hours are defined as persistent, whereas, those lasting more than 1 month are termed intractable. Although the exact underlying pathophysiology of hiccups is poorly understood, multiple causes, including gastric distension or gastroesophageal reflux, drugs, lesions or infections of the central nervous system, and irritation of the phrenic or vagus nerves, have been attributed to the etiology of hiccups (1). This is the case of a depressed patient with hiccups induced by aripiprazole.

Case Presentation

A 45-year-old single and illiterate woman with a well-balanced premorbid personality who has suffered from multiple depressive episodes from the age of 20. Each episode lasted about 8-12 months and resolved spontaneously. However, drug administrations failed to challenge. The last few depressive episodes, which occurred after the age of 40, were very severe compared to those she experienced when she was younger. Her quality of sleep and social life worsened. One of her sisters was the main source of support for hospital visits and drug follow-ups. Multiple antidepressants, excluding venlafaxine, and their combinations had previously been tried, but none of them were effective enough. She was not given any class of antipsychotics or mood stabilizers. Her psychiatric history did not include any hospital stays, thus, no electroconvulsive therapy was attempted.

When she was admitted to our adult psychiatry outpatient department, she was free of psychotropic treatment. In her first evaluation, a detailed history of psychiatric and medical

history was taken. Examination and blood screens of the patient did not reveal signs or symptoms of any underlying medical problems. Venlafaxine was administered and we planned to gradually increase the dose by 150 mg/day until her second visit. For her sleep problem, a 100mg dosage of trazodon was prescribed. Her second visit revealed some improvement, but she continued to experience sleeping problems. With the idea of accelerating improvement, 5mg of aripiprazole was added to treatment at night.

The day after the second visit, doctors received an urgent call from the patient's sister, saying the patient had developed a hiccup problem. Within 6 hours of taking aripiprazole, the patient started having continuous hiccups. She was consulted by the emergency department, who, after a preliminary examination, advised her to readmit to the care of a psychiatrist. After omitting aripiprazole from her prescription regimen, the hiccups stopped in approximately 66 hours. Upon a second administration of aripiprazole, the hiccups recurred within 6 hours. Aripiprazole was discontinued and a 225 mg daily dosage of venlafaxine was prescribed. The patient's depressive symptoms resolved without recurrence of hiccups within a month. The patient was maintaining well at her 3-month follow-up.

Discussion

Hiccups can arise from idiopathic, psychogenic and organic causes. The use of therapeutic drugs constitutes one of the important causes of hiccups (2). The neurotransmitters dopamine, serotonin and gamma amino butyric acid have been observed to play a significant role in the generation of hiccups. Induction of hiccups by dopaminergic agents and their successful treatment with antidopaminergic agents have been consistently reported (1,3). Stimulation of dopamine 3 (D3) receptors within the hiccup reflex arc may contribute to hiccups (4), which is reflected in case reports of hiccups associated with the administration of dopamine agonists

with high D3 affinities (5,6). Chlorpromazine, an antipsychotic and D2 antagonist, was found to be effective in alleviating hiccups and is the only medication approved by the Food and Drug Administration in this indication (7). Chlorpromazine may also derive benefits in treating hiccups from high D3 receptor affinity (8, 9). Aripiprazole stabilizes dopamine and serotonin concentrations through actions on the D2, 5HT1A, and 5HT2 receptors. Aripiprazole is also a partial agonist at D3 receptors and may result in hiccups via a similar mechanism to antiparkinsonian dopamine agonists (1). The literature suggests that aripiprazole-associated hiccups may be related to the sequence in which antipsychotics are trialed. As a partial agonist at the D2 and D3 dopamine receptors, aripiprazole can result in both hypo and hyperdopaminergic states, both of which have been implicated in hiccups. It was possible that a dystonic reaction of the diaphragm due to D2 blockade resulted in hiccups in this patient. Alternatively, aripiprazole's partial agonistic activity at the 5-HT1A receptor may have facilitated phrenic neuronal activity at the spinal cord level and therefore resulted in hiccups (1, 10, 11). In this case, the patient was antipsychotic naive prior to initiation of aripiprazole, and absence of antipsychotic sequence (9). Hiccups reported by authors resolve approximately in 72 hours after aripiprazole's discontinuation, and is associated with nearly 3-day half-life of the drug, which is 66 hours in this case (1). The clinicians should be cognizant that use of aripiprazole may be associated with hiccups. Additionally, due to the limited availability of literature describing occurrence of hiccups with aripiprazole, it was difficult to establish the rate of occurrence of this adverse event.

Conflict of Interest

The authors report no declarations of interest regarding the manuscript.

Authors' Contributions

Concept- M.E.O; Design- M.E.O., A.K.; Supervision- M.E.O., A.K.; Resource- M.E.O.; Materials- M.E.O.; Data Collection and/or Processing- M.E.O., M.H.O.; Analysis and/or Interpretation- M.E.O.; Literature Search- M.E.O., M.H.O.; Writing- M.E.O.; Critical Reviews- M.E.O., A.K.

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