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Hiccups associated with switching to aripiprazole from quetiapine in an adolescent patient

ABSTRACT

Aripiprazole has a distinct place amongst other antipsychotics with it's partial agonist-antagonist effect on dopaminergic and serotonergic receptors. There are several case reports associating aripiprazole to hiccups; but most of them are in adult age group. Exact pathophysiologic mechanisms underlying this side effect are still fairly unknown and case reports displaying this phenomenon in adolescent patients are scarce. We report an adolescent bipolar patient who developed hiccups right after panic-like symptoms while switching to aripiprazole from quetiapine. Switching from a more potent D2 and 5HT1A antagonist to aripiprazole seems to increase the risk of hiccup side-effect. It should be emphasized that, while using aripiprazole for the treatment of adolescent patients; clinicians should be careful about this rare and fairly unknown phenomenon, especially in the early stages of drug inititation and while increasing the dosage.

Keywords: Aripiprazole; dopamine; hiccup; serotonin

Ergen hastada aripiprazol'den ketiyapin'e geçiş ile ilişkili hıçkırık

ÖZET

Dopaminerjik ve serotonerjik reseptörler üzerindeki parsiyel agonist-antagonist etkisiyle aripiprazol, diğer antipsikotik ilaçlar arasında özel bir yere sahiptir. Aripiprazol kullanımı ile hıçkırık gelişimi arasındaki ilişkiyi bildiren birkaç olgu sunumu olmasına rağmen; bunların çoğu erişkin hastaları içermektedir. Bu durumun altında yatan patofizyolojik mekanizmalar tam olarak açıklanmamıştır ve ergen yaş grubundaki olgu sunumları kısıtlıdır. Bu çalışmada; aripiprazol tedavisinden ketiyapine geçiş sürecinde, panik-benzeri bulgular sonrasında hıçkırık yan etkisi oluşan bir ergen bipolar hastanın sunulması planlanmıştır. Daha güçlü D2 ve 5HT1A antagonisti bir psikofarmakolojik ajandan aripiprazole geçilirken, hıçkırık yan etkisinin oluşma riski artıyor gibi görülmektedir. Ergen hastalarda aripiprazol kullanılırken, özellikle ilaca başlanırken ve doz arttırılırken, klinisyenlerin bu görece nadir ve tam anlaşılamamış yan etki açısından dikkatli olmaları gerekmektedir

Anahtar Kelimeler: Aripiprazol; dopamin; hıçkırık; serotonin

Introduction

Hiccups are caused by sudden inspiration and then closure of the glottis right after repetitious spasmal contractions of the diaphragm and inspiratory muscles. It is often hard to determine the etiology of hiccups simply because wide variety of clinical conditions, such as gastric distension, gastroesophageal reflux or infections may cause them (1). Studies have shown that drugs that increase dopamine level may cause hiccups, whereas antidopaminergic drugs are used in the treatment of this condition (2,3). But conflicting with these findings, some researchers have reported hiccups caused by antidopaminergic drugs as well as Parkinson's disease itself (4).

In the literature; there is one case report of clozapine induced hiccups while olanzapine and sertraline were used in the treatment of hiccups in two separate case reports (5–7). When the pharmacodynamic profiles of olanzapine, sertraline and clozapine are taken into account; it is safe to say that, serotonin plays a role in the development of hiccups as well. With its partial dopamine agonist-antagonist effect; aripiprazole has a distinct place among all other antipsychotics. It has the highest affinity for 5-HT2B, D2 and D3 dopamine receptors; significant affinity for 5- HT1A, 5-HT2A, 5-HT7, 1A adrenergic and H1 histamine receptors; and the least affinity for 5-HT1D, 5-HT2C, 1B, 2A, 2B, 2C, 1 and 2 adrenergic, and H3 histamine receptors (8).

Even though hiccups are thought to be the results of complex interactions among the brain stem, respiratory areas in the brain, phrenic nerve nuclei, reticular formation and hypothalamus; most of the pathophysiological mechanisms underlying hiccups are still unknown. Review of the literature yielded total of fifteen studies regarding the possible involment of aripiprazole in the etiology of hiccups and only three cases were in adolescence (9–11). Reports regarding this issue in the adolescent patients are still scarce. Keeping this in mind; we aim to contribute to the understanding of this phenomenon by presenting an adolescent case who had panic-like symptoms and occurrence of hiccups after switching to aripiprazole from quetiapine.

Case

Our patient was 17 year old male who was admitted to our out-patient unit by his parents. Psychiatric anamnesis revealed that; he used to be a successful student in his school but his grades and

school attendance had decreased dramatically over the last several months. He had been feeling irritable for a period of time and occasionally having temper bursts in which he harmed himself by punching the walls and windows. He could not fall asleep most of the nights because he did not feel sleepy, he had been only sleeping for 2-3 hours each night and still did not need to sleep during the day. He was feeling anxious time to time and crying for no specific reason. He thought that his self-confidence was relatively low, but he was still overly involved in self-care routines and spending money on unnecessary things. He had been saving up his pocket money for a while then spent it all in one hour or so. He also stated that, even though he used to drink alcohol occasionally in the past, his drinking frequency had increased over the last 2 weeks. The patient had no previous psychiatry referrals in the past but he reported several time periods (could not remember the exact number or the time span) in which he felt like he was “invincible”, skipped school, involved in physical quarrels, slept less, spoke faster and harmed himself. Patient’s psychiatric evaluation showed mild acceleration of speech and thoughts, tangentialism in thought structure, irritable and depressive mood and the interview with his parents was also in line with his complaints. He did not have family history of any psychiatric illnesses. He scored 19 on Young Mania Rating Scale (YMRS) (12) and 40 on Child Depression Rating Scale (CDRS) (13); and he was diagnosed with bipolar I disorder, depressive episode with mixed features according to DSM-5 (14). Patient was initiated on quetiapine 50 mg/day treatment and it was gradually increased to 200 mg/day. After one month of quetiapine 200 mg/day treatment; he stated that he still could not sleep, felt more irritable and powerful and started to think about ways to kill himself. He scored 23 on YMRS and 47 on CDRS; so gradual discontinuation of quetiapine and initiation of aripiprazole was planned. Patient’s quetiapine was decreased to 100 mg/day and aripiprazole 2,5 mg/day was initiated.

On the next day after he was administered with aripiprazole 2,5 mg/day medication, he was referred to emergency unit with complaints of hiccups. His anamnesis revealed that he experienced acceleration of heart rate, shortness of breath, sweating and tremors on the first day of aripiprazole administration. On the second day of his treatment; his previously mentioned panic-like symptoms ceased but hiccups started and he had had hiccups for over 22 hours on the time of the referral. His

physical examination was normal, blood tests were in normal range and all of the physical and environmental causes of hiccups (such as head trauma, gastroesophageal reflux, infections) were ruled out. Naranjo scale was used to determine the probability score for the adverse reaction of hiccups related to aripiprazole and score was 7 (probable) (15). He was not administrated any specific medication for hiccups; his aripiprazole was discontinued and hiccups gradually stopped. His hiccups were attributed to the aripiprazole treatment, so he was started on risperidone treatment and dosage was gradually increased to 4 mg/day while his remaining quetiapine was discontinued. In the last psychiatric evaluation, his mood symptoms were under control, he was euthymic with no suicidal thoughts and he did not experience any hiccups with risperidone.

Discussion

Etiopathogenesis underlying hiccup occurrence during aripiprazole treatment still remains fairly unknown. Numerous neurotransmitters, mainly dopamine, serotonin and GABA, have been reported to play major roles in the pathophysiologic processes leading to hiccups (16). Especially case reports of successful treatment of hiccups with dopaminergic, anti-dopaminergic and anti-serotonergic medications prove these neurotransmitters' involvements (2–4,6). Aripiprazole is a fairly new and unique second generation antipsychotic with a distinct pharmacodynamic profile; and it has been reported to cause hiccups which is a rare side effect.

At the time of this case report; we were able to find total of fifteen studies implicating a relationship between hiccups and aripiprazole: Thirteen of them were case reports (9,10,16–26), one of them was a case series involving four cases (11) and one of them was a retrospective study involving seven cases (27). Two of these case reports have associated these findings to the decrease of blood sodium levels (21,23). Hyponatremia was reported to take several days to occur after drug administration (23), blood electrolyte levels of our patient was in the normal range and physical examination of the patient did not yield any symptoms or signs of hyponatremia. All other predispositions to hiccups, such as head trauma, gastroesophageal reflux or infections were ruled out.

When all of these facts are taken into account hyponatremia is probably not the main explanation of our case's hiccups.

Our patient did not have any side effects while using Quetiapine or when we switched to risperidone from apiprazole, but hiccups occurred after switching to aripiprazole from quetiapine. Quetiapine and risperidone are antagonists at both dopaminergic (D2) and serotonergic (5-HT2A, 5-HT1A, 5-HT1C, 5-HT1D) receptors while aripiprazole has partial agonist-antagonist effect on those receptors (28). This may reflect that neurotransmitter alterations caused by aripiprazole (mainly involving dopamine and serotonin) are the likely cause of hiccups in our case. This finding is in line with three case reports where the patients had hiccups with aripiprazole but not with quetiapine (16) or risperidone (19,25). Partial agonist-antagonist effect of aripiprazole on dopaminergic receptors may cause relatively increased or decreased dopaminergic levels compared to other antipsychotics; and since both high and low dopamine levels have been reported to be related to hiccups, it can be said that aripiprazole constitutes a higher risk profile for hiccups.

Our case report is distinct from others in the literature for the reason that hiccups started on the second day of medication right after he experienced panic-like symptoms. This symptomatology may be the proof of serotonergic distruption building up to occurrence of hiccups during aripiprazole treatment. This finding is, indeed, in line with the reports suggesting amelioration of persistent hiccups with olanzapine (5), sertraline (6,29) and tandospirone which is a new 5HT1A agonist (30). Although there are numerous evidence regarding serotonin's involvement in hiccup pathophysiology; exact mechanism is still unknown. It has been postulated that; in addition to the potential effect of D2 antagonism resulting in dystonic contractions of the diaphragm; partial activation on serotonergic receptors caused by aripiprazole (especially partial agonist-antagonist effect on 5HT1A) may lead to increased activity of phrenic neuron at the spinal cord level (2).

Re-challenging the pharmacological agent is needed in order to hold that drug responsible for a specific side-effect. There are only three case reports in which clinicians re-challenged aripiprazole after the hiccups are resolved (21,24,26); and two of them reported that hiccups re-occurred (21,24). We did not start over the aripiprazole treatment after our patient's hiccups are resolved, instead we

switched to risperidone. In this regard, our findings may be interpreted as not causal but occasional and should be approached by caution. However, when all of the previous studies are taken into account, switching from a more potent D2 and 5HT1A antagonist to aripiprazole seems to increase the risk of hiccup side-effect. It should be emphasized that, while using aripiprazole for the treatment of adolescent patients; clinicians should be careful about this rare and fairly unknown phenomenon, especially in the early stages of drug initiation and while increasing the dosage. We believe our case report will contribute to the literature in this matter.

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