Case Report

Aripiprazole-Induced Persistent Hiccups: A Case Report

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Aripiprazole is an antipsychotics medication that is widely used in clinical practice thanks to its safety profile and minor side effects; however, hiccups are a rare adverse event found in aripiprazole users. Hiccups can emerge from various origins including idiopathic, psychogenic and organic causes. Certain neurotransmitters are believed to be an etiology of hiccups especially dopamine and serotonin. This case report demonstrates a 15-year-old male adolescent with diagnosis of major depressive disorder with psychotic feature who developed persistent hiccups after initiating aripiprazole. The article discusses possible explanations of this incidence with clinical implication. Even though antipsychotics are credited to be an option of hiccups therapy, clinicians should be aware of antipsychotic-induced hiccups especially aripiprazole.

Keywords: *Aripiprazole, Hiccups, Aripiprazole-induced hiccups, Drug-induced hiccups, Antipsychotics*

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Aripiprazole is a novel antipsychotic launched in 2002 which act as dopamine partial agonist and serotonin stabilizer. Because of its unique profile, it is an effective medication in both positive and negative psychotic symptoms. Although aripiprazole shows some minor side effects such as restlessness or drowsiness, hiccups are rarely reported in aripiprazole users. In general, most antipsychotics are thought to be one of hiccup treatment medication; aripiprazole has been reported to produce hiccups[1]. Nowadays, the exact pathophysiology of hiccups is not clearly known, but the neurotransmitters dopamine and serotonin are believed to play crucial role. Moreover, hiccups can happen by idiopathic, psychogenic or organic cause which clinician should concern these origins. In this article, author will present a 15-year-old adolescent who developed hiccups after initiating aripiprazole and discuss possible causes of this incident.

Case Report

A 15-year-old male adolescent came to hospital with problem of recurrent emotional outburst for one month. He showed a depressed mood from being bullied at school and sometimes had suicidal thoughts with paranoid delusion of his friends insulting him. He was deeply stressed and tried to harm himself. He also reported auditory hallucination about his friends blaming him and sometimes refused to attend school. His parents revealed that he was an anxious child since he was toddler and had a hard time adjusting himself to new environment.

Previous history showed that he was diagnosed with attention deficit hyperactivity disorder (ADHD) and anxiety disorder seven years ago. He has been taken methylphenidate 20 mg/day and fluoxetine 20 mg/day for controlling his inattentive and anxiety symptoms, respectively. On initial assessment, mental status examination revealed that he had a depressed and anxious mood with paranoid delusion and auditory hallucination. Diagnosis of major depressive disorder with psychotic feature with comorbidity ADHD and anxiety disorder were made following Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[2]. Fluoxetine dosage was increased to 40 mg/day with addition of aripiprazole 5 mg/day to alleviate psychotic symptoms. Methylphenidate was held to prevent aggravating psychotic symptoms.

Three hours after first tablet of aripiprazole, he had continuous hiccups which lasted for 48 hours and parents decided to cease aripiprazole and hiccups disappeared six hours afterward. He and his parents visited psychiatric clinic again to notify psychiatrist about his decision to stop aripiprazole. Consequently, psychiatrist did physical and neurological evaluation and worked up for blood chemistry which showed normal findings (Serum sodium level = 136 mEq/L).

Forty-eight hours after hiccups stopped, aripiprazole was rechallenged again at 2.5 mg/day after informing consents. There is no recurrence of hiccups again after following up him for six month. Depressive

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and psychotic symptoms were also improved with aripiprazole 2.5 mg/day and fluoxetine 40 mg/day without new incidence of emotional outburst.

Discussion

Hiccups are brief and involuntary spasmodic contraction of the diaphragm and glottic closure and cause to blocking of air entry into trachea[3]. Because hiccups were presented more than 48 hours, it can be classified as persistent hiccups[4] which can lead to other medical morbidities such as esophagitis, depression, weight loss and malnutrition[5]. Hiccups have various etiologies such as gastric distension or gastroesophageal reflux, drugs, lesions or infections at central nervous system, and irritation of phrenic or vagus nerves[6]. Furthermore, certain medication or metabolic imbalances which affect dopamine, serotonin, opioid, calcium channel and gamma-aminobutyric acid (GABA) pathways in the brainstem and medulla can produce hiccups[7,8]. Even though most hiccups are benign and resolve by themselves, clinician should acknowledge causes of persistent hiccups due to their complexity in origin.

Aripiprazole is a novel antipsychotic which affect as a partial agonist with D2 and D3 dopamine receptors[9]. Besides, it has effect with serotonergic receptor by partial agonist with 5-HT1A and partial antagonist with 5-HT2A receptor[10]. Due to dual-neurotransmitter mechanism, aripiprazole is a drug of choice in various psychiatric disorders. It does not show certain serious side effects such as extrapyramidal movement or weight gain like other antipsychotics, but it has minor side effects such as dizziness, restlessness and drowsiness. Although hiccups are barely seen after initiating aripiprazole, there were certain articles published since the first two cases were reported by Behere et al[11] and Ginsberg[12] in 2007 which concluded that hyponatremia might attribute to hiccups in patients using aripiprazole. There was a significant correlation between hyponatremia and hiccups in hospitalized patient[13]. Also, in patient with chest infection and post-operative cancer surgery, hiccups might be an initial signal of hyponatremia[14]. Researchers still do not know an exact pathophysiology of this phenomenon.

However, there were some reports hypothesized that brain injury might affect this rare adverse event[15,16]. In the meantime, there were various cases showing that aripiprazole could induce hiccups without brain injury or hyponatremia causation which considers that aripiprazole might affect directly with neurotransmitters causing to hiccup especially dopamine and serotonin[1,17,18]. Surprisingly, hiccups occurred from either antidopaminergic agent such as perphenazine[19] or dopaminergic agent such as levodopa[20,21]. Some case reports came to conclusion that switching from other antipsychotics to aripiprazole can result in hiccups due to imbalance of dopaminergic states[1,10,16].

In summary, following this case report, the onset and disappearance of hiccups are correlated with aripiprazole which suggest the possibility of adverse drug reaction. Although the pathophysiology of aripiprazole-induced hiccups is unclear, it is hypothesized that hiccups originate from three causes. Primary, persistent hyperdopaminergic state resulted from methylphenidate may lead to hiccups. This patient has been taking methylphenidate which acts as dopamine reuptake inhibitor after more than seven years; therefore, he was in chronic hyperdopaminergic state. Rapidly switching from methylphenidate to aripiprazole which is partial dopamine agonist, provokes dysregulation of dopamine and leads to hiccups. Theoretically, D2 dopamine receptor blocking agents such as antipsychotics especially chlorpromazine can inhibit hiccups, but aripiprazole which is a D2 partial agonist at lower doses can generate hiccups[22]. Author hypothesizes that chronic use of methylphenidate co-occurring with rapidly change to aripiprazole may aggravate hiccups in this patient.

Secondary, serotonin 5HT1A receptor agonist and 5HT2A receptor antagonist effects from aripiprazole, enhance phrenic motor neuron activity at the level of the spinal cord and can lead to hiccups[23]. These are supported by evidence of serotonergic medication. For example, buspirone which is a 5HT1A receptor agonist cause of hiccups[15]. In contrast, tandospirone, which is a 5HT1A receptor antagonist, is effective in treating hiccups[24]. Even though, serotonin receptor agonists cause of hiccups, some serotonergic medication can be used in hiccups therapy. These are emerging from some reports of successful treatment by serotonin agents such as sertraline, olanzapine and clozapine[3,19,20,25]. On the other hand, increasing dopamine release both directly from D2 dopamine agonist and indirectly from serotonin 5HT1A agonist and serotonin 5HT2A antagonist could induce hiccups[15]. As a result, the author hypothesizes that aripiprazole-induced hiccups in this patient are from both dopaminergic and serotonergic dysregulation.

Lastly, drug-drug interaction between fluoxetine and aripiprazole attribute to hiccups. In other

words, increasing plasma level of aripiprazole is resulted from fluoxetine (17). Elimination of aripiprazole is mainly through hepatic metabolism including two cytochrome P450 isoenzymes (CYP2D6 and CYP3D4). Fluoxetine which is a strong CYP2D6 inhibitor could hinder aripiprazole elimination and lead to escalation of its plasma level[25]. As a consequence, increasing plasma level of aripiprazole may aggravate possibility of adverse event such as hiccups in this case report. Clinicians should be aware of aripiprazole-induced hiccups when prescribing it with other psychotropic medications which affect aripiprazole elimination, especially fluoxetine.

Conclusion

A 15-year-old male adolescent with diagnosis of major depressive disorder with psychotic features developed persistent hiccups after initiating aripiprazole 5 mg/day. Hiccups disappeared after discontinuation of the medication and there was no report of hiccups after rechallenging aripiprazole at 2.5 mg/day. The etiology is unclear about this rare incidence, but the author believes that neurotransmitters such as dopamine and serotonin play an important role. Because of aripiprazole dual-neurotransmitter effect, it is more likely to cause hiccups than any other antipsychotics. Further studies are required to explore correlation between hiccups and aripiprazole. Even though aripiprazole-induced hiccups can resolve spontaneously without treatment, clinician should prevent this unexpected incidence by starting aripiprazole with low dose and slow titration with frequent monitoring of hiccups.

What is already known on this topic?

Until present, there is no well-established explanation of aripiprazole-induced hiccups, but there are some case reports discussing possible etiologies. Further research is needed to explore this incident.

What this study adds?

This is the first case report of aripiprazole-induced hiccups in Southeast Asia. Clinicians should acknowledge this rare incident before prescribing aripiprazole. Starting with low dose and slowly titrating, and informing patients about possible drug reaction, may help clinicians deal with it.

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Potential conflicts of interest

None.

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ภาวะสะอึกต่อเนื่องจากยา aripiprazole: กรณีศึกษาผู้ป่วย

ทรงภูมิ เบญญากร

Aaripiprazole เป็นยารักษาโรคจิตที่ใช้กันอย่างแพร่หลายเนื่องจากมีความปลอดภัยและผลข้างเคียงต่ำ แต่ภาวะสะอึกเป็นผลข้างเคียงอันหนึ่งที่พบได้น้อยมากในผู้ใช้ aripiprazole ภาวะสะอึกสามารถเกิดได้จากหลากหลายปัจจัย เช่น สาเหตุทางจิตใจ สาเหตุทางกาย หรือในบางครั้งก็ไม่สามารถหาสาเหตุได้ ในรายงานผู้ป่วยฉบับนี้ได้นำเสนอกรณีศึกษาผู้ป่วยวัยรุ่นอายุ 15 ปีวินิจฉัยเป็นโรคซึมเศร้าและมีอาการทางจิตที่มีภาวะสะอึกหลังจากเริ่มใช้ aripiprazole บทความนี้อภิปรายถึงสาเหตุที่น่าจะเป็นไปได้ร่วมกับความเกี่ยวข้องในทางคลินิก แม้ว่ายารักษาโรคจิตจะถูกนำมาใช้ ในการรักษาภาวะสะอึก แพทย์ควรระมัดระวังถึงอุบัติการณ์ของภาวะสะอึกที่อาจเกิดจากยาดังกล่าวโดยเฉพาะอย่างยิ่งยา aripiprazole