



Risperidone-Induced Hiccups in an Adolescent

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Hiccups are involuntary spasmodic contractions of the diaphragm and inspiratory intercostal muscles followed by sudden closure of glottis which leads to halting the start of an inspiration. There are many factors which may cause hiccups. Although the exact pathophysiological processes involved have not yet been established, the neurotransmitters dopamine, serotonin and gamma amino butyric acid (GABA) have been documented to play a significant role in the generation of hiccups. Here, we present a case of risperidone-induced hiccups in a 14-year old adolescent to discuss the probable causes, the etiology and the clinical outcomes of this side effect.

Keywords: Adolescent, Hiccups, Risperidone

Introduction

Hiccups are involuntary spasmodic contractions of the diaphragm and inspiratory intercostal muscles followed by sudden closure of glottis which leads to halting the start of an inspiration [1]. The neurobiologic reflex system of hiccup includes the vagus and phrenic nerves, and the sympathetic chain from thoracic segments T6–T12 in the afferent limb; and the brain stem, hypothalamus, the respiratory center, medullary reticular formation, phrenic nerve nuclei in the efferent limb. The C3–C5 segments and the brain stem form the main link between the efferent and the afferent limbs [2].

It is called intractable persistent hiccup when the duration of hiccup exceeds 48 h [3]. There are many factors which may cause hiccups. Vagus and phrenic nerve irritation (resulting from e.g., tumors, goiters, cysts, gastroesophageal reflux disease, hiatal hernia), central nervous system disorders (e.g., trauma, infection, structural, or vascular lesions), toxic metabolic disorders (e.g., medications, general anesthesia, alcohol abuse, diabetes, gout, electrolyte deficiencies), psychogenic factors (e.g., anxiety, stress, excitement) are main categories of possible mechanisms that lead to persistent hiccups

[1]. Although the exact underlying mechanisms have not been established, gamma amino butyric acid (GABA), serotonin, and dopamine have been shown to have a role as an etiological factors for hiccups [2, 4].

Hiccups caused by dopaminergic agents and treatment with antidopaminergics have been reported [1, 5, 6]. The serotonin's role for producing hiccups is thought because of reported treatment of hiccups by olanzapine and sertraline. Also there is a report for clozapine that causes hiccups [3, 7, 8].

Risperidone is an atypical antipsychotic, used for psychotic disorders, behavioral problems and tic disorders in childhood. It has the strongest affinity for D2 dopamine and 5-HT2 receptors; strongest affinity for α 1 adrenergic, M muscarinic and H1 histamine receptors. The main mechanism of action of risperidone is known to be the blockage of serotonin and dopamine systems through actions especially at the D2 and 5-HT2 receptors [10, 11]. Risperidone has a adverse effect profile as extrapyramidal symptoms, increased weight, and metabolic problems.

We are going to present a risperidone-induced hiccups case to discuss the probable etiological mechanisms, the causes, and the clinical outcomes of this side-effect.

Case Report

A 14-year-old girl who had been referred to psychiatry outpatient clinic from pediatric nephrology department with complaints of irritable mood, diminished interest in daily activities, fatigue and feeling of worthlessness for about a month. At last days, she complained about hearing voices, which had been calling her name. She suffered from chronic renal failure diagnosed nearly 2 years ago. Recently, she was given hemodialysis. Her blood and urine analysis had been shown no recent pathological sign, including electrolyte imbalance. The psychiatric examination revealed depressed affection, psychomotor retardation and auditory hallucinations. We put the diagnosis of major depressive episode with psychotic features according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria [12]. She was started on risperidone 0.5 mg/day. Within 2-3 h after taking risperidone, the patient started to have hiccups. The hiccup didn't disappear on that day. We evaluated all other possible organic causes, including neurologic examination for acute neurologic problems, physical, blood and urine examinations for acute infections and sudden medical causes. We also asked to her and her parents about history of drinking carbonated beverages, alcohol, eating too much in last two days. We couldn't find any cause explaining the hiccups. We discontinued risperidone after 60 hours and the hiccups ended a day later. There were no hiccups following 3 days.

Because of this, further analysis were not done and we decided to restart a risperidone. After restart of risperidone, the hiccups begin again within a few hours. Risperidone was ordered to stop, immediately. And again, after 12-14 hours the hiccups disappeared. There were no hiccups following two weeks.

Discussion

Our case describes the possible role of risperidone for inducing hiccups. It is one of the rare reports in the literature [13] documenting this fact. Previously, hiccups resulting after aripiprazole and clozapine treatment were reported [2, 3]. As we mentioned earlier, risperidone has the strongest affinity for D2 dopamine and 5-HT₂ receptors; strongest affinity for α ₁ adrenergic, M muscarinic and H₁ histamine receptors. The main mechanism of action of risperidone is known as the blockage of serotonin and dopamine systems at the D₂, 5-HT₂ receptors [11]. Risperidone also has adverse effects as extrapyramidal symptoms, increased weight, and metabolic problems.

In contrast to the previous reports of hiccups caused by antipsychotics, electrolyte disturbances (e.g. hyponatremia) seem to be an unlikely etiology in our patient [14]. Although our patient had a kidney problem, the electrolyte and biochemical analysis were normal during the presence of hiccups. According to these, we offer the modulation of neurotransmitters as a possible mechanism for the hiccups after risperidone in our patient. And also the beginning time, lasting time, and relationship between drug discontinuation and hiccups are compatible with literature [2, 13].

As both hypo- and hyperdopaminergic states have been asso-

ciated with the development of hiccups, the antagonism of dopamine by risperidone may be the cause. But, the obvious neuronal mechanism through which dopamine effects the hiccup reflex circle remains unknown.

The other possible mechanism is through serotonin which has a role in the underlying process of hiccups. Risperidone has an action on 5HT₂ receptor, but the consequence of hiccups through this action also remains unclear.

Conclusion

The duration and relationship of hiccups with risperidone and the absence of any neurologic and physical signs and symptoms seem to ignore the systemic cause for the hiccups. Although hiccup is a benign side effect, it can be very stressful and may cause disruption of treatment. More studies are needed to understand mechanism of neurotransmitters involved in the hiccup reflex system and the pathways for the different medications effects.

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