

CASE REPORT

Persistent hiccups due to aripiprazole in an adolescent with obsessive compulsive disorder responding to dose reduction and rechallenge

Meryem Ozlem Kutuk¹, Ali Evren Tufan², Gulen Guler^{3,*}, Veli Yildirim³, and Fevziye Toros³

¹Department of Child and Adolescent Psychiatry, Baskent University Medical and Research Center, Adana 01000, Turkey, ²Department of Child and Adolescent Psychiatry, Abant İzzet Baysal University Medical Faculty, Bolu 14000, Turkey, and ³Department of Child and Adolescent Psychiatry, Mersin University Medical Faculty, Mersin 33000, Turkey

*Correspondence address. Department of Child and Adolescent Psychiatry, Mersin University Medical Faculty, Mersin 33190, Turkey. Tel: +090-3242410000-2164; +905075093592; Fax: +90-3242410092; E-mail: dr.gulen@hotmail.com

Abstract

Our case involves persistent hiccup arising in an adolescent with obsessive compulsive disorder (OCD) who was using aripiprazole as an augmentation to fluoxetine and whose hiccups remitted with dose reduction and rechallenge. Treatment suggested that aripiprazole might lead to hiccups. Antipsychotics are also used for the treatment of hiccups, but recent case reports suggest that they cause hiccups as well. Within 12 h of taking 5 mg aripiprazole, the 13-year-old girl began having continuous hiccups, which lasted for 3–4 h. The hiccups resolved when the dose of aripiprazole was reduced to 2.5 mg. To achieve augmentation, aripiprazole was replaced with risperidone 0.5 mg/day for 1 month, but excess sedation was observed. As a result, aripiprazole was restarted at a dose of 2.5 mg/day, and 1 week later, it was increased to 5 mg/every other day. No hiccups were observed.

INTRODUCTION

'Hiccup' is a repetitive, involuntary, spasmodic and characteristic sound that appears with sudden closure of the glottis as a consequence of involuntary contraction of the diaphragm and respiratory muscles [1]. Although the pathophysiological processes that cause hiccups have not been fully determined, central nervous system disorders, gastrointestinal disorders such as gastric distension and reflux, head and neck diseases, metabolic disorders, electrolyte disorders and some drugs are posited as causes of hiccups [1].

Among drug-induced hiccups, aripiprazole, a dopaminergic stabilizing agent, is often cited, both for transient and persistent

hiccups among adult and adolescent patients [2–6]. As far as we are aware, hiccups in these patients arose while switching treatments and did not involve dose titration and rechallenge. Here, we present persistent hiccups arising in adolescent with obsessive compulsive disorder (OCD) who was using aripiprazole as an augmentation to fluoxetine and whose hiccups remitted with dose reduction and rechallenge.

CASE REPORT

The patient was a 13-year-old girl who was referred to the out-patient clinic with complaints of controlling, counting, a need

Received: December 30, 2015. Revised: March 1, 2016. Accepted: March 2, 2016

© The Author 2016. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

for symmetry and excessive washing. She was diagnosed with OCD 4 years ago by a child and adolescent psychiatrist and has received sertraline up to 200 mg/day along with intermittent exposure response prevention for 4 years, with no significant benefit. Mental status examination revealed obsessions of doubt, symmetry, ordering, contamination and religiosity, checking, ordering and mental compulsions along with depressive symptoms. Developmental milestones were normal with no evidence of tics. Family history revealed maternal OCD with a positive response to fluoxetine. Baseline psychometric evaluations revealed C-YBOCS and CGI-S scores of 35 and 6, respectively. Accordingly, the diagnosis of OCD was confirmed, and sertraline was cross-tapered with fluoxetine up to 60 mg/day on the 16th week of treatment. Evaluation at the 4th month revealed C-YBOCS and CGI-S scores of 31 and 5, respectively, which suggests minimal benefit. Aripiprazole 5 mg/day was added therefore, for augmentation. The patient and her family reported that persistent hiccups started 12 h after the initial dose and continued for a week. After this, the parents immediately reduced the dose to 2.5 mg/day, leading to the cessation of hiccups. To achieve augmentation, aripiprazole was replaced with risperidone 0.5 mg/day for 1 month, but excess sedation was observed. Consequently, aripiprazole was restarted at 2.5 mg/day. One week later, the dose was increased to 5 mg/every other day with no occurrence of hiccups. She was followed for 8 weeks without hiccups, and her C-YBOCS and CGI-S scores were found to be 15 and 3, respectively, denoting treatment response. Evaluation with the Naranjo algorithm revealed a score of 7 (probably adverse drug reaction) [7].

DISCUSSION

Here, we report a female adolescent with OCD who developed persistent hiccups with aripiprazole augmentation of fluoxetine treatment, whose hiccups remitted with dose reduction and did not appear with a rechallenge. Although previous reports of persistent and transient hiccups with aripiprazole exist, our case is unique in that the adverse reaction responded to dose reduction and did not appear with rechallenge [2–6]. Although the exact roles of neurotransmitters within the reflex arc of hiccups are not known, antipsychotics are used in the management of hiccups [8]. Existing data suggest that both dopamine and serotonin may play a role in the generation of hiccups [2–6,8]. Previous reports posited that both hypo- and hyper-dopaminergic states may lead to hiccups [2–6,8]. However, there are several other alternative explanations in our case. First, elimination of aripiprazole involves two cytochrome P450 isoenzymes (CYP2D6 and CYP3A4) and fluoxetine, which is a potent inhibitor of CYP2D6, can block the metabolism of aripiprazole and increase its blood levels [9]. Second, partial agonistic at 5-HT_{1A} and antagonistic effects at 5-HT_{2A} receptors of aripiprazole within the spinal cord at the level of the phrenic nerve, perhaps potentiated by fluoxetine, may have caused the hiccups [10]. Lastly, as posited before, either hypo- or hyper-dopaminergic states may cause hiccups as shown before [2–6]. The temporal profiles of hiccups in our patient, their remission with dose reduction and their lack of re-occurrence

with challenge, suggest, however, a mechanism of potentiation of its effects probably via CYP450. Regardless of exact etiology, it may be prudent for the clinicians to be aware of this rare adverse effect.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

There were no sources of funding.

ETHICAL APPROVAL

No approval is required.

CONSENT

The patient's parent signed consent was obtained.

GUARANTOR

M.O.K. is the guarantor of this paper.

REFERENCES

1. Full-Young C, Ching-Liang L. Hiccup: mystery, nature and treatment. *J Neurogastroenterol Motil* 2012;**18**:123–30.
2. Hori H, Nakamura J. Hiccups associated with switching from olanzapine to aripiprazole in a patient with paranoid schizophrenia. *Clin Neuropharmacol* 2014;**37**:88–9.
3. Yeh YW. Persistent hiccups associated with switching from risperidone to aripiprazole in a schizophrenic patient with cerebral palsy. *Clin Neuropharmacol* 2011;**34**:135–6.
4. Ray P, Zia ULHaq M, Nizamie SH. Aripiprazole-induced hiccups: a case report. *Gen Hosp Psychiatr* 2009;**31**:382–4.
5. Silverman MA, Leung JG, Schak KM. Aripiprazole-associated hiccups: a case and closer look at the association between hiccups and antipsychotics. *J Pharm Pract* 2014;**27**:587–90.
6. Bilgic A, Yilmaz S, Yilmaz E. Hiccups associated with aripiprazole in an adolescent with bipolar disorder. *J Child Adolesc Psychopharmacol*. June 2015, ahead of print. doi:10.1089/cap.2014.0138.
7. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–45.
8. Nishikawa T, Araki Y, Hayashi T. Intractable hiccups (singultus) abolished by risperidone, but not by haloperidol. *Ann Gen Psychiatry* 2015;**14**:13.
9. Travis MJ, Burns T, Dursun S, Fahy T, Frangou S, Gray R, et al. Aripiprazole in schizophrenia: consensus guidelines. *Int J Clin Pract* 2005;**59**:485–95.
10. Zimmer MB, Goshgarian HG. Spinal activation of serotonin 1A receptors enhances latent respiratory activity after spinal cord injury. *J Spinal Cord Med* 2006;**29**:147–55.