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İbrahim Duvarci & Mustafa Yilmaz

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Persistent Hiccups After Switching from Zuclopenthixol to Aripiprazole

İbrahim Duvarci¹, Mustafa Yılmaz²

¹Muğla Üniversitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, Muğla - Turkey

²Muğla Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, Muğla - Turkey

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Dear Editor,

Hiccups occur as a result of involuntary, intermittent and spasmodic contractions of the diaphragm and aspiratory muscles. Short-term hiccups are of no clinical significance. However, the condition is defined as persistent hiccups, if it continues for longer than 48 hours. Hiccups may occur as a result of organic, psychogenic or idiopathic factors. Metabolic disorders, electrolyte imbalances, pneumonia, pathologies of the central nervous system, injuries/irritation of vagal or phrenic nerve, laryngitis, goiter and gastroesophageal reflux are the leading causes among organic factors (1). Some drugs are known to cause hiccups. Dopamine, serotonin and GABA have been suggested to have an important role, although the exact mechanism is unknown (2).

Our case is a 66-year-old, married and retired man. His complaints began 7 years ago. He had had delusions of reference and persecution, delusion of mind reading, bizarre and delusional behavior and auditory hallucinations. The patient did not have any insight and therefore had never been taken to a psychiatrist. In the last year, psychotic symptoms increased in frequency and in severity and his paranoid delusions towards his wife became threatening. He was then persuaded by his relatives to attend the psychiatry outpatient clinic. The patient was diagnosed to have schizophrenia according to the DSM-IV criteria. The patient had a past medical history of diabetes mellitus and was being treated with insulin and oral antidiabetic therapy. Also the

patient's suffered from coronary artery disease and had undergone a coronary artery by-pass graft operation in 2005. His cousin has also been receiving treatment for psychosis. Zuclopenthixol oral drops 4 mg/day was initiated and, upon the absence of any side effects, was titrated to a dose of 5 mg/day at his 2-week repeat visit. After administration of zuclopenthixol, his clinical picture rapidly and almost completely recovered; the patient acquired partial insight into his condition and no drug-related side effects were observed. However, in the 7th month of the treatment, the patient developed bradykinesia, mild hand tremor, oral-buccal dyskinesia, psychomotor retardation and dysphoric mood. These side effects were thought to be related to zuclopenthixol and, without dose tapering, the patient was switched to 10 mg/day aripiprazole, an atypical antipsychotic drug. One week later, the patient was admitted to the emergency room with the complaint of persistent hiccups, which was thought to be caused by recently administered aripiprazole and thus, the drug was discontinued. At day 4, after discontinuation of aripiprazole, the hiccups completely disappeared. The patient was dropped from follow-up in the outpatient clinic after the hiccups disappeared.

Etiologic investigation of persistent hiccups should begin with organic causes. Internal and neurologic examination revealed normal findings and blood chemistry was within normal ranges. Myocardial ischemia is known to cause persistent hiccups (3). The patient was found to be stable after being examined in the center, where he underwent his coronary by-pass operation. The reason for persistent hiccups in this case, seems to be aripiprazole therapy. Hiccups appeared 2 days after initiation of the drug and completely disappeared 4 days after cessation. A possible pathophysiological mechanism was thought to be related to dopamine. The patient was on zuclopenthixol therapy for 7 months. Zuclopenthixol is a typical antipsychotic and its primary mechanism of action is dopamine (D2) blockade. Long-term use causes upregulation of post-synaptic D2 receptors. This upregulation is known to play a role in dyskinesia (4). Aripiprazole

therapy initiated afterwards may have caused hiccups through agonistic effects on already upregulated D2 receptors (5). Similar to our case, a case of persistent hiccups after switching from risperidone to aripiprazole has been reported (6). Hiccups disappeared in this case after discontinuation of aripiprazole and re-administration of risperidone. Aripiprazole is also a partial agonist of 5HT1A receptors. This agonistic effect may have increased phrenic nerve activity and therefore caused hiccups (5,7). In another case of persistent hiccups reported in the literature, hiccups occurred after addition of

aripiprazole to carbamazepine therapy for organic affective disorder (8). Additionally, hiccups have been reported to have occurred after initiation of aripiprazole therapy and this was suggested to be caused by drug-related hyponatremia (9). Persistent hiccups may occur after switching to aripiprazole therapy in patients receiving long-term therapy with typical anti-psychotics. In this regard, persistent hiccups should be considered a side effect in the spectrum of extrapyramidal symptoms/dyskinesia.

Best Regards

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