

Aripiprazole-Induced Enuresis in a Child with Autistic Disorder

Otizm Tanılı Bir Çocukta Aripiprazole Bağlı Enürezis

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ABSTRACT

Aripiprazole is being increasingly reported to be effective in treating behavioral problems of children with autism. It has fewer side effects with respect to other atypical antipsychotics. However, to our knowledge, in the literature, there is no report on aripiprazole-induced enuresis in children and adolescents diagnosed with autism, although enuresis has been a very rare adverse event observed during the premarketing evaluation of oral aripiprazole. Here, we present a sixteen-year-old boy with diagnosis of autism and epilepsy who developed enuresis after starting aripiprazole and had rapid remission after the discontinuation of the drug. (*Archives of Neuropsychiatry 2011; 48: 164-6*)

Key words: Aripiprazole, enuresis, autism, children

ÖZET

Aripiprazolün otistik çocuklarda görülen davranışsal problemleri tedavi etmede etkili olmasıyla ilgili yayınların sayısı giderek artmaktadır. Aripiprazolün diğer atipik antipsikotiklere nazaran daha az yan etkisi bulunmaktadır. Oral aripiprazol henüz piyasaya sürülmeden önce yapılan değerlendirmelerde enürezis çok nadir bir yan etki olarak gözlenmesine rağmen, bilindiği kadarıyla yazında, otizm tanılı çocuk ve ergenlerde aripiprazole bağlı enürezis ile ilgili bir vaka bildirimi yoktur. Biz bu yazıda on altı yaşında otizm ve epilepsi tanısı ile takip ettiğimiz, aripiprazole başladıktan sonra enürezisi olan ve ilacı kestikten sonra alt kaçırmayı hızla düzelen bir olgu sunduk. (*Nöropsikiyatri Arşivi 2011; 48: 164-6*)

Anahtar kelimeler: Aripiprazol, enürezis, otizm, çocuk

Introduction

Aripiprazole anovel atypical antipsychotic, is being administered to children and adolescents for the management of mood instability, aggression, and psychosis. Recently, the U.S. Food and Drug Administration (FDA) has approved it for the treatment of irritability associated with autistic disorder in pediatric patients aged 6-17 years and including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (1). Compared to other atypical antipsychotics, aripiprazole is reported to cause fewer side effects e.g., weight gain, elevation in glucose and lipid levels, prolactin elevation, QTc prolongation, and onset of diabetes mellitus. Other untoward events include headache, insomnia, nausea, vomiting, lightheadedness, somnolence, constipation, increased appetite and dyspepsia (2). Here, we present a case of aripiprazole-induced enuresis in an adolescent with autistic disorder.

Case Report

H, a nonverbal 16-year-old male, was brought to our outpatient clinic by his parents due to his aggressiveness and self-injurious behaviors. Information regarding his developmental and psychiatric history was taken from his mother. According to her, he was diagnosed with autistic disorder due to his severe impairment in language development and social-emotional reciprocity, and repetitive behaviors when he was 3. His medical history was also positive for epilepsy. He was on valproic acid 2000 mg/day and lamotrigine 100 mg/day since the age of 12. Risperidone was initiated at 0.5 mg/day to cope with his behavioral problems, but ceased because of excessive vomiting and gastrointestinal problems. Thus, we switched to olanzapine 5 mg/day. However, he began to have epileptic seizures soon after olanzapine treatment, so the medication was stopped. Then, he was given quetiapine, haloperidol and escitalopram, respectively, but all these drugs also induced epilepsy by

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decreasing the seizure threshold. Hence, we decided to use aripiprazole to control the symptoms and he was given aripiprazole 10 mg/day. But, he developed new-onset diurnal enuresis within the first day of the treatment and it continued 10-15 times a day till we stopped the medication a week later. His medical history and workup, including physical and neurological examination and urinalysis, were unremarkable. The patient had urinary bladder control at 3 years of age, and he and his family had no previous history of urinary incontinence. His enuresis resolved rapidly after discontinuation of aripiprazole. We then decided to restart aripiprazole to understand whether the diurnal enuresis was associated with the use of aripiprazole or not. Enuresis reemerged on the first day of the treatment and repeated 10-15 times a day again. Meanwhile, he benefited from aripiprazole and his behavioral symptoms resolved substantially without emerging an epileptic seizure, but we could not keep up the treatment because his parents requested the discontinuation of aripiprazole due to the severity of enuresis, thus, we ceased aripiprazole a week after the beginning and decided to switch to pimoziide.

Discussion

We reported the case of an autistic patient who developed diurnal enuresis after starting aripiprazole and had rapid remission after the discontinuation of the drug. Although antipsychotic-induced enuresis may be more common than generally reported (3), urinary incontinence associated with aripiprazole has been a very rare adverse event observed during the premarketing evaluation of its oral form.

Possible mechanisms have been described in the pathophysiology of antipsychotic-induced enuresis. They include decreased internal bladder sphincter tone due to alpha 1 adrenergic blockade (4), reduced dopamine transmission in the basal ganglia (5), urinary retention and subsequent overflow incontinence due to antimuscarinic properties of antipsychotics (6) and blockade of pudendal reflexes via antagonism of 5-HT₂ or 3 (7) and the activation of neuronal 5-HT₄ receptors in the detrusor muscle (8). The sedative effects of antipsychotics may also lead to inability to wake up during sleep and might cause enuresis (9).

Moreover, efficacy of aripiprazole is mediated through a combination of partial agonist activity at D₂ and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D₂, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects. Aripiprazole exhibits high affinity for dopamine D₂ and D₃, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine D₄, serotonin 5-HT_{2C} and 5-HT₇, alpha₁-adrenergic and histamine H₁ receptors (K_i values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC₅₀>1000 nM) (2).

The antagonist activity of aripiprazole at 5-HT_{2A} and alpha 1 receptors on detrusor muscle and internal bladder sphincter, respectively, might have contributed to enuresis in our case,

although it had no noticeable anticholinergic effects. As serotonin can indirectly potentiate cholinergic neuromuscular transmission in isolated human detrusor muscle strips (10) and there are a number of case reports on SSRI-induced enuresis (11-14), aripiprazole may be responsible for enuresis because of its serotonin reuptake properties (SERT). Besides, possible reduced dopamine transmission due to partial agonist activity of aripiprazole at D₂ receptors might also cause urinary incontinence in our autistic case despite the fact that the other partial agonist activity at 5-HT_{1A} receptors can reduce bladder dysfunction, while selective 5-HT_{1A} antagonists inhibit bladder contraction (15).

On the other hand, aripiprazole had no clinically important interactions with the drugs, valproic acid and lamotrigine, which our patient was using (2). Because enuresis remitted rapidly after discontinuation of aripiprazole and reemerged after starting again, the improvement of enuresis in this case cannot be explained by the other drugs. Our patient was using these antiepileptics for four years and there was no dose increase that may contribute to the emergence of enuresis. Moreover, the risk of seizures with aripiprazole is reported to be 0.1%, the lowest among atypical agents (1,2).

It is known that antipsychotic-induced enuresis happens to be mostly a transient and time-limited phenomenon (16,17). As our case had severe behavioral problems and communicational difficulties and his parents did not cope with the severity of enuresis, we could not apply behavioral treatment and could not continue to use aripiprazole.

Urinary incontinence associated with aripiprazole seems to be very rare like the other cases with antipsychotic-induced enuresis (18) and our autistic case is probably the first report according to literature (PubMed). Additionally, there are two case reports describing the efficacy of combined use of aripiprazole in the treatment of clozapine-induced enuresis (19).

However, the use of aripiprazole has become widely common in treating behavioral problems associated with autistic spectrum disorders; thus, our case report shows that aripiprazole-induced enuresis should be born in mind when using this drug especially in children with developmental disabilities. However, further research is needed to better understand the pathophysiology of enuresis with aripiprazole.

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