Aripiprazole for Maladaptive Behavior in Mental Retardation: Case Reports

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ÖZET:

Zekâ geriliğinde görülen davranış sorunları için aripiprazol: Olgu bildirimleri

Aripiprazol özgül farmakolojik özelliklere sahip yeni bir antipsikotik ilaç olup, kısmi dopamin agonisti olarak etkinlik gösteren ve üçüncü kuşak antipsikotik olarak isimlendirilen dopamin sistem dengeleyicisidir. Bu makalede zekâ geriliği olan üç ergende görülen davranış sorunlarının aripiprazol ile tedavi sonuçları sunulmaktadır. Bu olguların ikisi zekâ geriliği ve yaygın gelişimsel bozukluk tanısı, biri yalnız zekâ geriliği tanısı ile aripiprazol 5-10 mg/gün dozlarında tedaviye alınmıştır. Bir aylık ilaç tedavisi yanıtı Sorun Davranışlar Kontrol Listesi, Conners Ana-Baba Derecelendirme Ölçeği, Klinik Global İzlenim – Değişim Ölçeği ile; ilaç yan etkileri UKU Yan etki Derecelendirme Ölçeği ile değerlendirilmiştir. Aripiprazol'ün bu üç olguda iyi tolere edilmiş ve belli düzeylerde etkinlik göstermiş olması zihinsel yetersizliği ve yaygın gelişimsel bozukluğu olanlarda güvenli ve etkili olabileceği yönünde değerlendirilmiştir. Klinik ölçümlere göre ancak bir hastanın tedaviye yanıt verdiği söylenebilse de diğer iki olguda da olumlu değişiklikler (kısmi yanıt) izlenmiştir. Kısa tedavi süresi, görece düşük ortalama tedavi dozlarına rağmen bu sonuçlar tedavisi güç hasta grubunda aripiprazolün bir tedavi seçeneği oluşturabileceğine işaret etmektedir. Etkinlik ve güvenlik konularını inceleyen gelecekteki klinik çalışmalar aripiprazolün bu hasta grubunda yeni bir tedavi seçeneği olup olamayacağı sorusuna yanıt verebilecektir.

Anahtar sözcükler: Aripiprazol, zeka geriliği, çocukluk çağı ruhsal bozuklukları, tedavi

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ABSTRACT:

Aripiprazole for maladaptive behavior in mental retardation: case reports

Aripiprazole is a new psychotropic agent that possesses a unique pharmacologic profile. The drug demonstrates partial dopamine agonist activity and has been labeled a third-generation antipsychotic and dopamine system stabilizer. We report on the use of aripiprazole in the treatment of maladaptive behaviors in three individuals (cases) with mental retardation. Three adolescents (two was (were) diagnosed as mental retardation and pervasive developmental disorder, one was diagnosed as mental retardation) received an open-label trial of aripiprazole with 5 to 10 mg/day. Drug response was evaluated by using the Aberrant Behavior Checklist, Conners Parent Rating Scale and Clinical Global Impressions- Improvement Scale first month after treatment. Side effects were followed by UKU Side Effect Rating Scale. Aripiprazole was well tolerated and somehow effective in all of the cases and appears to be a safe and efficacious alternative in the management of patients with both intellectual disabilities and pervasive developmental disorders. Only one of the patients was taken as treatment responder according to definition, the other two also had a slight improvement in clinical sense. Though short duration of treatment and relatively lower drug doses these results with aripiprazole indicate a probable treatment option in this difficult-to-treat population. Clinical studies are needed to clarify the effectiveness and safety of this medication.

Key words: Aripiprazole, mental retardation, child mental disorders, treatment

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INTRODUCTION

Atypical antipsychotics have been tried to treat aggression, hyperactivity, agitation, irritability, stereotypy and self-injurious behaviors in children and adolescents with mental retardation (MR), pervasive developmental disorders (PDD) and conduct disorder (1,2,3). Risperidone is the most studied drug and found to be effective for the treatment of aggression, self-injury, and agitation in children with autistic disorder and disruptive behavior disorders associated with MR (4,5).

Aripiprazole is a novel atypical antipsychotic which is a partial agonist of dopamine D2 and serotonin 5-HT1A, and a 5-HT2A antagonist. It is reported to cause fewer side effects than other atypical antipsychotics, e.g., weight gain, elevation in glucose, lipid, prolactin levels and prolongation of QTc. A few reports in children and adolescents suggested that aripiprazole was associated with improvement in aggression, self-injurious behaviors and hyperactivity in MR and PDD (6,7,8). Reported adverse effects included weight gain, transient dizziness, increased aggression, stiffness, myalgias, facial dyskinesia, diarrhea, headache, insomnia, and sleepiness. Sleepiness was the only adverse effect to have a dose-response relationship. Besides, overdose was related to cause only early nausea and vomiting followed by prolonged lethargy in young children and is well tolerated by adolescents (9).

The effectiveness and safety of aripiprazole in three children (adolescents) with MR and PDD were evaluated in this study.

METHOD

Study involved 3 patients with mental retardation with severe behavior problems. Two of them also had a diagnosis of PDD. Diagnoses were made by two child and adolescent psychiatrists, using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; (10). In all 3 cases, treatment with an atypical antipsychotic had recently been discontinued due to lack of effectiveness and/or significant adverse effects. Three cases were given aripiprazole and were evaluated at first visit and at the end of one month treatment by the same clinician. All three families have been informed about presenting the clinical status of their children for scientific purposes.

Assessment tools:

Clinical Global Impressions- Improvement (CGI-I) Scale is rated from 1 to 7 (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse). In the case series described below, patients with CGI-I rating of 1 or 2 were described as treatment responder (11).

Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale evaluates 48 symptoms in 4 categories and other side effects related to antipsychotics. Clinician assessed magnitude of symptoms, perceived causality and degree of disability (12).

Conners Parent Rating Scale (CPRS) is answered using four-option Likert-scale items in 4 subscales. High scores obtained with the scale indicate the intensity of the symptoms specific to disruptive behavior disorder (13,14).

Aberrant Behavior Checklist (ABC) is a 58-item rating scale with five subscales. It was validated in Turkish on mentally retarded children and adolescents, aged between 10 and 24. Twelve items of 58 were excluded from the ABC-Turkish version because of same factor loading. In this study ABC-Turkish version was used (15, 16).

Case 1 is a 10 year-old male. His first referral to child and adolescent psychiatry outpatient clinic was due to hyperactivity, stereotypic behaviors and hyperventilation as a self- stimulating behavior since he was 6. It has been learned that he had an ongoing difficulty with social interaction, restricted social reciprocity, preference to be alone, rocking, hand clapping and epileptic seizures. According to his parents, his language development regressed after an epileptic attack at age of 18 months. His intelligence was evaluated with Bayley test at age 4 and his diagnosis was severe mental retardation (IQ: 20). At age 10 he was able to use nearly four words to the purpose. He was taking special education since he was 4 years old. He had interfering symptoms like hyperactivity, irritability, and stereotypic movements. He diagnosed as severe mental retardation and pervasive developmental disorder not otherwise specified (PDD-NOS) with associated interfering behaviors. He had a history of previous drug trials including adequate doses of imipramine, haloperidole, methylphenidate IR, thioridazine, chlorpromazine, risperidone, zuclopenthixol and quetiapine. These treatments were either unsuccessful or could not be continued due to side effects such as increased frequency of epileptic seizures, extrapyramidal symptoms and/or weight gain. His last treatment was quetiapine (300 mg/day), clobazam, gabapentin and valproate. Due to inadequate previous treatment response and persisting severe disruptive behavior, aripiprazole was given at 5 mg/day. His body weight was 37 kg and height was 136 cm at baseline. At follow up there had been no weight change. According to UKU Side Effect Rating Scale he had increased salivation, decreased sleep time but none of these were affecting functionality. CGI-I Scale score was 3

Table 1: Pre and post trial scores for ABC

	Case 1		Case 2		Case 3	
ABC	Pre-trial	Post-trial	Pre-trial	Post-trial	Pre-trial	Post-trial
Irritability,agitation, crying	36	30	16	7	8	9
Lethargy and social withdrawal	29	30	12	8	10	7
Stereotyped behavior	9	9	3	1	3	3
Hyperactivity and noncompliance	5	4	5	3	0	0
Inappropriate speech	6	8	2	4	4	0

Table 2: Pre and post trial scores for CPRS

CPRS	Case 1		Case 2		Case 3	
	Pre-trial	Post-trial	Pre-trial	Post-trial	Pre-trial	Post-trial
Inattention	7	6	9	4	7	8
Hyperactivity	6	8	5	3	8	6
Oppositional behavior	0	0	7	3	3	8
Conduct disorder	7	7	12	4	6	8
Total score	20	21	33	14	24	30

(minimally improved). His CPRS and ABC scores (Table 1 and 2) were not changed pre and post treatment.

Case 2 is a 16 year-old male. His first referral to child and adolescent psychiatry clinic was due to hyperactivity, inattention, underachievement in school, difficulties in peer relations, rituals like placing his books, pencils under his pillow when going to bed, lack of spontaneous speech and social reciprocity, preference to be alone, screaming at lessons, asking preservative questions, talking by himself, aggressive behaviors since he was 7. His developmental stages were delayed. His WISC-R verbal, performance and full scale scores were 50, 55 and 50 respectively at the age of 8. He was taking special education since he was 8 years old. He was diagnosed as mild mental retardation and PDD-NOS with associated interfering behaviors. He had a history of previous drug trials including adequate doses of imipramine, methylphenidate IR, thioridazine, risperidone, concerta (methylphenidate), and ziprasidone. These treatments were either insufficient to control interfering symptoms or could not be continued due to side effects such as enuresis, sedation and/or weight gain. Due to inadequate treatment response and persisting severe symptoms aripiprazole was given at the dosage of 10 mg/day. His body weight was 65 kg and height was 162 cm at first visit. His weight increased 2 kg per month. According to UKU Side Effect Rating Scale he had increased sleep, constipation, weight gain and headache however; none of them was affecting his functioning. CGI-I Scale score was 2 (much improved). Clinically his improvement was prominent in social relations, oppositional behaviors and irritability. However his self-injurious behaviors did not respond to treatment. His improvement was also verified by parents in the ratings of CPRS and ABC. The results were given in Table 1 and 2. Overall evaluation showed he was the most improved patient in the study group.

Case 3 is a 13 year-old female. Her referral to child and adolescent psychiatry clinic was due to school failure, difficulties in peer relations, excessive and inappropriate speech, impulsive behaviors, disinhibition of sexual behaviors, and increased interest in sexuality. Her developmental stages were delayed. Her WISC-R verbal, performance and full scale scores were 52, 48 and 47 respectively at the age of 12. She was taking special education since she was 10. She was diagnosed as mild mental retardation and interfering impulsive behaviors. She had a history of previous drug trial of risperidone (1 mg/day). Risperidone was insufficient to control interfering symptoms and caused significant weight gain. Due to side effects and inadequate response to prior medications, aripiprazole was given at 5 mg/day. According to UKU Side Effect Rating Scale she had increased sleep, skin eruption however, none of them was affecting his functionality and skin eruption was not found as caused by the drug. CGI-I Scale scores was 3 (minimally improved). However her ABC factor scores were showed little improvement for lethargy and excessive speech factors.

DISCUSSION

This study reveals that our clinical experience with aripiprazole in difficult-to treat patients. Though the given dosages would not be optimized due to the minor side effects during the clinical trial, all three patients were shown comparable clinical improvement. Two patients showed “minimal” and one showed “much” improvement that was taken as treatment responder examined by CGI-I rating. In this study, Aripiprazole was also fairly well-tolerated and the most common side effect was sedation without any interference with daily functioning supporting the results of other studies in children with MR or PDD using aripiprazole treatment (6,7,8). A fairly new retrospective naturalistic study including 34 severely impaired children with PDD treated with aripiprazole has similiar results as our study (17). In this study,

aripiprazole monotherapy was associated with a significant improvement in maladaptive behaviours measured by CGI-I in one-third of patients. Agitation and insomnia were the most frequent seen adverse effects. Beside the effectiveness of aripiprazole in children with MR or PDD, there are also some initial data on the use of aripiprazole in young patients with Tourette's Disorder and with bipolar disorder showing significant response and good tolerability (18,19,20).

This was an open- label study which aimed to diminish target behavioral symptoms related with MR. The trial resulted in a slight improvement according to CPRS and ABC scores. Despite these promising preliminary results it is important to remember that the case series was conducted in a naturalistic, unblinded and uncontrolled fashion. Another limitation to this study is the sample size and the short duration of treatment with lower doses.

This presented case series of three pediatric mentally retarded patients illustrates that aripiprazole has the potential to be an effective and well-tolerated treatment that should be validated by controlled clinical studies with larger samples.

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