

## Use of Aripiprazole in Clozapine Induced Enuresis: Report of Two Cases

This report describes the efficacy of combined use of aripiprazole in the treatment of a patient with clozapine induced enuresis. Aripiprazole acts as a potential dopamine partial agonist and the dopamine blockade in the basal ganglia might be one of the causes of urinary incontinence and enuresis. We speculate that aripiprazole functioned as a D2 agonist in hypodopaminergic state of basal ganglia caused by clozapine and maintained dopamine level that would improve enuresis ultimately.

**Key Words :** Clozapine; Enuresis; Aripiprazole; Dopamine

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## INTRODUCTION

Clozapine is an effective drug for the treatment of refractory schizophrenia. It has a few extrapyramidal side effects and rarely leads to tardive dyskinesia, but it can induce agranulocytosis, seizures, sedation, obsessive-compulsive symptoms, weight gain, and sialorrhea. In addition, urinary system side effects, especially enuresis, occur in 6% to 44.3% of patients (1, 2). These side effects can cause medical complications, contribute to noncompliance, and consequently decrease the quality of life of patients.

The mechanisms of enuresis caused by clozapine include overflow incontinence after urinary retention due to the antimuscarinic action of clozapine (3), the cholinomimetic activity of clozapine (4), and decreased internal urethral sphincter tone caused by an  $\alpha$ -1 adrenergic blockade effect (5). In addition, enuresis has been attributed to non-specific clozapine action such as its excessive sedative action, the lowering of the seizure threshold, and constipation exacerbating urinary retention and overflow (6). Based on these mechanisms, treatments such as decreasing the dose of clozapine, replacing it with other antipsychotic drugs with low anticholinergic effects, and using tricyclic antidepressants, trihexyphenidyl, oxybutynin, and ephedrine have been used, but contrary results have been reported (4, 5, 7-9). The specific mechanisms of clozapine-induced enuresis have not been determined. Kantrowitz has reported that risperidone-induced enuresis improved after changing from risperidone to aripiprazole or olanzapine, and after stopping the nighttime dosage. He explained that mechanisms for enuresis included adrenergic blockade via  $\alpha$ -1

and blockade of pudendal reflexes via antagonism of 5-HT<sub>2</sub> or 3 (10).

In addition, antipsychotic-induced enuresis can be explained by decreased dopamine transmission in the basal ganglia or an imbalance between dopamine and norepinephrine within the basal ganglia (11). Here, we report two cases in which combination treatment with clozapine and aripiprazole, a dopamine partial agonist that works as a D2 antagonist in a hyperdopaminergic state and as a D2 agonist in a hypodopaminergic state (12), was used effectively for patients with clozapine-induced enuresis.

## CASE REPORTS

### Case 1

A 52-yr-old man was diagnosed with paranoid type schizophrenia at age 18. Although he had been hospitalized for treatment several times, auditory hallucinations, persecutory delusions, and delusions of reference persisted, and he was treated with clozapine 350 mg/day after being hospitalized in the Psychiatry Department of Inha University Hospital in December 1997. Because his psychotic symptoms improved with no side effects except sialorrhea, he was discharged from the hospital on the 26th day of hospitalization and treated as an outpatient. During outpatient treatment, he responded to his drugs well and his symptoms were stable. While receiving clozapine 200 mg/day and amitriptyline 25 mg/day for sialorrhea in June 1998, he experienced enuresis two

to three times per week. Although behavioral education such as limiting water intake after 20:00 and urinating before going to bed, and treatment with bethanechol 5 mg/day were somewhat effective, enuresis one to three times per week persisted. After starting combination treatment with clozapine 200 mg/day and aripiprazole 10 mg/day from 5 mg/day initially in May 2005, he had no enuresis from August 2005, and the aripiprazole was stopped in September. Subsequently, enuresis two to three times per month was observed in November 2005, and clozapine 200 mg/day and aripiprazole 10 mg/day orally recommenced in January 2006; subsequently, enuresis ceased. After discontinuing the aripiprazole in May 2006, at the patient's request, enuresis started again (approximately two times per week), but no enuresis occurred in December 2006.

## Case 2

A 27-yr-old man diagnosed with paranoid type schizophrenia at age 14 had been hospitalized for treatment several times, but his persecutory delusions and violent behavior persisted. Treatment using clozapine was started in September 1997 when he was hospitalized at Seoul National University Hospital. Considering the distance to the hospital, he was transferred to the Psychiatry Department of Inha University Hospital for treatment in September 1997. Because the administration of clozapine 250 mg/day led to some improvement in his symptoms, and no side effects except sialorrhea were observed, he left the hospital on the 42nd day of hospitalization. During outpatient treatment, persecutory ideation and sialorrhea continued. In August 1999, he experienced a convulsion while taking clozapine 425 mg/day and benztropine 3 mg/day. In August 2000, he had a second convulsion while being treated with clozapine 400 mg/day and benztropine 3 mg/day. Obsessive-compulsive symptoms began in August 2001 and persisted; the patient took fluvoxamine 100 mg/day in August 2002 and discontinued benztropine in November 2002. In August 2003, while taking clozapine 450 mg/day and fluvoxamine 100 mg/day, enuresis occurred two to three times per week. Despite treatment with clozapine 400 mg/day, benztropine 2 mg/day, and fluvoxamine 100 mg/day, along with behavior education, he experienced enuresis nearly every day. The enuresis improved in April 2005, after he was treated with clozapine 300 mg/day, benztropine 2 mg/day, fluvoxamine 50 mg/day, and aripiprazole 10 mg/day. Since May 2005, he had been taking clozapine 350 mg/day, benztropine 2 mg/day, fluvoxamine 50 mg/day, and aripiprazole 15 mg/day, and no enuresis occurred. In August 2005, the aripiprazole was discontinued because the patient said that he became sick and nervous after taking it; subsequently, he had no enuresis. In March 2006, enuresis was observed once to twice per month; subsequently, he took additional aripiprazole 10 mg/day and had no enuresis with no change in previous medications.

## DISCUSSION

In the first case, enuresis began six months after administering clozapine and persisted for seven years. Combination treatment with aripiprazole without reducing the clozapine dose had a rapid effect, and the enuresis disappeared in three months. Subsequently, the enuresis improved or worsened repeatedly according to whether the patient was taking or not taking aripiprazole, respectively. Although the occurrence of enuresis could reflect transient episodes (6), it was thought to be related to the treatment effect of aripiprazole, based on the temporal relationship between the administration of aripiprazole and the occurrence of enuresis. In addition, even with combination treatment with amitriptyline, which has been used to treat enuresis (8), the enuresis began somewhat later contrary to the results of previous studies, that reported that it began within several hours to two to four weeks after using clozapine (13). Therefore, the occurrence of enuresis should be monitored, even when the patient is on a stable dose of clozapine.

In the second case, the patient experienced enuresis after taking clozapine for six years, and it continued for approximately 20 months. Subsequently, it improved in one month following combination treatment with aripiprazole. Subsequently, the enuresis improved or worsened repeatedly, according to whether the patient was taking or not taking aripiprazole, respectively.

Although combination treatment with benztropine and a selective serotonin reuptake inhibitor can increase urinary incontinence and the risk of enuresis (14), there is little relationship between enuresis and benztropine and fluvoxamine, considering the timing of benztropine and fluvoxamine intake and the timing of enuresis. The improvement of enuresis in this case cannot be explained by aripiprazole alone because the dose of clozapine was also decreased in the combination treatment. However, the enuresis improved soon after administering aripiprazole, and it did not recur after increasing the dose of clozapine to the previous level. Moreover, when enuresis recurred, without changing previous medications but after adding aripiprazole, enuresis improved in one month. Therefore, the aripiprazole was thought to be related to the improvement in the clozapine-induced enuresis. The patient also experienced enuresis relatively late in his treatment, which indicated the need for continuous monitoring of the occurrence of enuresis.

The treatment effects of aripiprazole on clozapine-induced enuresis could be attributed to the specific pharmacological action of dopamine partial agonists. Ambrosini suggested that urinary continence is correlated with the catecholamine system within the basal ganglia and reported that drugs that increase noradrenergic activity and dopamine agonists improve enuresis because it occurs in a hypodopaminergic and noradrenergic-deficit state (11). In addition, diseases that decrease dopamine within the basal ganglia, e.g., Parkinson's disease

and Creutzfeldt-Jakob disease, can cause urinary incontinence and enuresis, and the administration of amantadine, a dopamine agonist, improves enuresis (15, 16). In our patients, we speculate that aripiprazole functioned as a D2 agonist in the hypodopaminergic basal ganglia caused by clozapine and maintained a dopamine level that ultimately improved the enuresis.

Moreover, considering that selective 5-HT<sub>1A</sub> antagonists inhibit bladder contraction (17), aripiprazole, which is a 5-HT<sub>1A</sub> partial agonist, could reduce bladder dysfunction compared to clozapine. In addition, because aripiprazole has a small  $\alpha$ -1 adrenergic blockade effect and little antimuscarinic effect or sedative action, even combination treatment with two neuroleptics would not worsen the enuresis.

This case study is meaningful because it presents cases in which clozapine-induced enuresis was improved using combination treatment with aripiprazole. More systemic studies are needed to determine the specific effects of aripiprazole on clozapine-induced enuresis.

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