Efficacy of Low-Dose Aripiprazole to Treat Clozapine-Associated Tardive Dystonia in a Patient With Schizophrenia

Lyang HUH[1], Bong Ju LEE[2]

SUMMARY

Tardive dystonia (TDt) is a debilitating side effect of long-term antipsychotic treatment. Even though TDt is associated with increased psychiatric morbidity, mortality, and severely decreased quality of life, there are no treatment modalities for TDt. Clozapine has been used as a treatment option for TDt in patients with schizophrenia. Interestingly, several recent case reports have indicated that it can enhance or induce TDt. We report a case of clozapine-associated TDt that was treated with low-dose aripiprazole (0.5 mg/day). The patient was a 51-year-old Korean woman with schizophrenia that had been admitted to the psychiatric ward for her florid psychotic symptoms. The patient's TDt symptoms began to develop after 1 year of clozapine (200 mg/day) treatment. Her motor symptoms improved markedly after adding low-dose aripiprazole (0.5 mg/day) to clozapine (175 mg/day). Aripiprazole is a dopamine D2 receptor partial agonist that exhibits partial agonistic activity against serotonin-1A (5-HT1A) receptors and full antagonistic activity against 5-HT2A receptors. The dopaminergic tone in the surrounding milieu is important for aripiprazole activity. In addition, antioxidative effects of aripiprazole may manage the neurotoxic effects of clozapine. To our knowledge, only one report has described a patient with clozapine-associated TDt that was treated with moderate doses of aripiprazole (10–15 mg). This case report may be the first report of low-dose aripiprazole treatment of clozapine-associated TDt.

Keywords: Aripiprazole, Clozapine, Tardive dystonia, Schizophrenia

INTRODUCTION

Antipsychotic medication-induced tardive dystonia (TDt) is a debilitating side effect of schizophrenia treatment (Adityanjee et al. 1993). Once TDt is recognized, the clinician should consider reducing the dose of the antipsychotics or even stopping the medication altogether. Alternatively, the clinician may switch the patient to clozapine or a newer antipsychotic (Charfi et al. 2004). Other strategies, such as the use of tetrabenazine and trihexyphenidyl, are helpful (Simpson 2000). However, these agents are useful in only 40-50% of TDt patients (Bhidayasiri et al. 2011). We report a case of clozapine-associated TDt in a patient with schizophrenia that was resolved with treatment of low-dose aripiprazole.

CASE

A 51-year-old Korean woman was treated with antipsychotic medications for schizophrenia symptoms. She had a history of auditory hallucinations, persecutory delusions, aggressive speech, and behavior that presented in her mid-20s. She was treated with haloperidol for 10 years, and then with pimozide for 4 years. However, she was not drug compliant. After several drug-free months, she relapsed with severe psychotic symptoms and was treated with 6 mg risperidone for 3 weeks. She developed acute dystonia; therefore, risperidone (6 mg/day) was changed to aripiprazole (25 mg/day). However, her psychotic symptoms were difficult to control and she was admitted to our inpatient psychiatric ward. No response to the increased aripiprazole dose was detected and the psychotic symptoms relapsed. She stabilized after switching back to risperidone with a dose increase to 8 mg/day. However, she developed a sudden tongue protrusion and orofacial dyskinetic movements. She was started on clozapine, which was increased to 200 mg/day. She began to show improvement and the tardive dyskinesia symptoms resolved completely after 4 weeks. The Abnormal Involuntary Movement Scale

Received: 03.06.2015 - **Accepted:** 07.03.2016

[1]Resident, [2]Assoc. Prof., Department of Psychiatry, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea(South)

e-mail: *bongjulee@empal.com*

score dropped from 15 to 0. She remained symptom free after discharge. Unfortunately, after 12 months of clozapine therapy, she gradually developed dystonic posturing of the neck in December 2014. The dystonia persisted despite adding 2 mg benztropine and reducing clozapine to 175 mg/day. There was no family history of neurological disorders including dystonia. Investigations including brain magnetic resonance imaging, electroencephalogram, and hematological studies (such as complete blood count, liver, renal, and thyroid function tests, blood prolactin level, blood glucose level, copper, ceruloplasmin, antinuclear antibody test, hepatitis B surface antigen, hepatitis C antibody test) did not reveal any abnormalities. As the tardive dystonia persisted, low-dose aripiprazole (0.5 mg/day) was added to the 175 mg/day clozapine in February 2015. The patient stated in a 4 week follow-up that her TDt symptoms improved markedly. At that time, the total Extrapyramidal Symptom Rating Scale score for dystonia dropped from 4 to 0. She remained free of psychotic symptoms and abnormal movement with clozapine (175 mg/day), aripiprazole (0.5 mg), and benztropine (2 mg) daily.

DISCUSSION

TDt occurs more frequently in men and other associated risk factors are adolesence, mental retardation, convulsive therapy, and a history of acute dystonia (Ryu et al. 2015; van Harten et al. 1999). The pathophysiology of TDt is still not well understood. Although the neuropharmacological changes underlying TDt remain to be elucidated, several hypotheses have been proposed to understand TDt. A possible role for serotoninergic and noradrenergic modulation of cholinergic pathways has been suggested for patients with TDt (Remington 1988). Another popular hypothesis is that repetitive stimulation of D1 receptors by endogenous dopamine sensitizes D1-mediated striatal output in the presence of D2 receptor blockade (Burris et al. 2002; Mailman 2010).

Low affinity for striatal D2 receptors and the anti-serotonergic (5HT2 and 5HT1c) and anti-cholinergic effects of clozapine have been suggested as a possible mechanism for its therapeutic effects in patients with tardive syndromes (Richelson 1999; Bolden et al. 1991). Although clozapine is the most common choice used to treat TDt, it has been associated with the development of TDt (Bruneau et al. 1998; Duggal et al. 2007; Garca-Lado et al. 2005; Huang et al. 2012; Hung et al. 2007; Mendheka et al 2011 Molho et al. 1999). The neurotoxic hypothesis has also been proposed based on preclinical models of clozapine-induced tardive syndrome. Administration of clozapine is associated with an increase in reactive oxygen species similar to haloperidol (Fehsel et al. 2005; Moghaddam et al. 1990). Hence, clozapine may exert neurotoxic effects through the production of reactive oxygen species.

Aripiprazole is a dopamine D2 receptor partial agonist with partial agonistic activity at the serotonin-1A (5-HT1A) receptors, and antagonistic activity at the 5-HT2A receptors (Burris et al. 2002). Due to its unique mechanism of action, aripiprazole has a dopamine stabilization effect and normalizes dopamine upregulation (Inoue et al. 1997). Aripiprazole is a 5-HT1A partial agonist that activates the 5-HT1A-auto

Table 1. Summary and comparison of different cases with tardive dystonia

	The present Case	Duggal et al. (2003)	Garcia-lado et al. (2005)	Huang et al. (2012)	Hazari et al. (2014)
Sex / Age	51-year-old woman	45-year-old woman	30-year-old woman	42-year-old woman	54-year-old man
Diagnosis	Schizophrenia	Schizoaffective disorder, bipolar type	Paranoid schizophrenia	Refractory schizophrenia	Delusional disorder
Previous Treatment & response	Haloperidol, Pmozide, Risperidone, Aripiprazole, Clozapine Showed much improvement	Depot haloperidol, risperiode	Haloperidol, olanzapine	Full dose of aripiprazole, paliperidone, quetiapine, amisulpiride, ECT Showed limited improvement	Risperidone 6mg Remission state
Treatment side effects	Dystonic posturing of the neck emerged (Tardive dystonia)	Mild Tardive dystonia	Dystonic contraction (Tardive dystonia)	Tonic flexion of the neck to the right, with medial rotation	Orofacial dyskinesia, blepharospasm, cervical dystonia, chorieform movements of extremities
Medication changes	Low-dose (0.5mg/day) aripiprazole was added to clozapine	Risperidone and divalproex were restarted. (No response) Aripiprazole 15 mg daily was added	Clozapine treatment was initiated and increased to 100 mg/day	Added aripiprazole 30 mg/day	Clozapine treatment was initiated and increased to 175 mg/day
Response to newly treatment	Tardive dystonia was improved	Within 3 days, choreoathetosis was dramatically reduced.	Marked decreased in dystonic contraction	Torticollis partially improved. Not worsen with increasing of clozapine to 325 mg/day	Improvement in his movement disorder and showed progressive improvement

receptor, causing increased release of dopamine (Eskow et al. 2007). Aripiprazole has been shown to have antioxidative effects on antipsychotics through modulating the generation of microglial produced superoxide (Kato et al. 2011). These mechanisms may explain the improvement of symptoms in patients with clozapine-associated TDt after the administration of aripiprazole.

Very few reports are available on clozapine-induced TDt (Hazari et al. 2014; Huang et al. 2012); both reported different characteristics than other case reports (Duggal et al. 2003; Garcia-lado et al. 2005) (Table 1). One case study suggested that adding aripiprazole (15-30 mg/day) improves TDt caused by clozapine (Huang et al. 2012). However, cases of aripiprazole-induced TDt have also been reported (De Berardis et al. 2013; Oommen et al. 2006). Reports on the effectiveness of aripiprazole as a treatment for TDt are a topic of great debate.

Previously, we reported that low-dose aripiprazole was effective on TD (Huh et al. 2015). The present case suggests the effectiveness of adding low-dose aripiprazole in the management of clozapine-associated TDt. However, the exact mechanism of the beneficial effects of aripiprazole on clozapine-associated TDt is not well understood. The therapeutic effect has been attributed to the partial agonism of D2 and 5-HT1A receptors as a dopamine stabilizing effect (Inoue et al. 1997). Additionally, antioxidative effects of aripiprazole by modulating microglial superoxide generation have also been suggested as a possible mechanism.

However, the risks of aripiprazole merit caution. Controlled studies are needed to further determine the role of aripiprazole when treating clozapine-associated TDt in patients with schizophrenia.

REFERENCES

Adityanjee, Lindenmeyer JP (1993) Precipitation of dystonia by m-CPP in a schizophrenic patient treated with haloperidol. Am J Psychiatry 150:837–8

Bhidayasiri R, Boonyawairoj S (2011) Spectrum of tardive syndromes clinical recognition and management. Postgrad Med 87:132–41.

Bolden C, Cusack B, Richelson E (1991) Clozapine is a potent and selective muscarinic antagonist at the five cloned human muscarinic acetylcholine receptors expressed in CHO-K1 cells. Eur J Pharmacol 192: 205–6.

Bruneau MA, Stip E (1998) Metronome or alternating Pisa syndrome: a form of tardive dystonia under clozapine treatment. Int Clin Psychopharmacol 13:229–32.

Burris KD, Molski TF, Xu C et al (2002) Aripiprazole a novel antipsychotic is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther 302:381-9.

Charfi F, Cohen D, Houeto JL et al (2004) Tardive dystonia induced by atypical neuroleptics: a case report with olanzapine. J Child Adolesc Psychopharmacol, Spring 14:149-52.

De Berardis D, Serroni N, Moschetta FS et al (2013) Reversal of aripiprazole-induced tardive akathisia by addition of pregabalin. J Neuropsychiatry Clin Neurosci, Spring: 25:E9-10.

Duggal HS (2003) Aripiprazole-induced improvement in tardive dyskinesia. Can J Psychiatr, Dec 48:771-2

Duggal HS, Mendhekar DN (2007) Clozapine-induced tardive dystonia (blepharospasm). Neuropsychiatry Clin Neurosci, Winter:19:86-7.

Eskow KL, Gupta V, Alam S et al (2007) The partial 5-HT(1A) agonist buspirone reduces the expression and development of l-DOPA-induced dyskinesia in rats and improves l-DOPA efficacy. Pharmacol Biochem Behav 87:306-14.

Fehsel K, Loeffler S, Krieger K et al (2005) Clozapine induces oxidative stress and proapoptotic gene expression in neutrophils of schizophrenic patients. J Clin. Psychopharmacol 25:419–26.

Garca Lado I, Garca Caballero A, Recimil JM et al (2005) Reappearance of tardive dystonia with olanzapine treated with clozapine. Schizophrenia Research 76:357-8.

Hazari N, Grover S, Kate N et al (2014) Management of tardive syndrome with clozapine: A case series. Asian J Psychiatr, April vol8:111-4.

Huh L, Lee BJ (2015) Efficacy of aripiprazole in antidepressants-induced tardive dystonia and tardive dyskinesia: a case report. Psychiatr Danub, Jun;27:195-7.

Hung TH, Lee Y, Chang YY et al (2007) Reversible Pisa syndrome induced by clozapine: a case report. Clin Neuropharmacol 30:370–2.

Huang WL, Chang HC, Tsai YF et al (2012) Aripiprazole augmentation for clozapine-associated tardive torticollis. The J Neuropsychiatr and Clin Neurosci 24:4 E49

Inoue A, Miki S, Seto M et al (1997) Aripiprazole, a novel antipsychotic drug, inhibits quinpirole-evoked GTPase activity but does not up-regulate dopamine D2 receptor following repeated treatment in the rat striatum. Eur J Pharmacol 321:105-11.

Isabel GL, Alejandro GC, Maria JR et al (2005) Reappearance of tardive dystonia with olanzapine treated with clozapine. Schizophrenia Res, Jul 15:76(2-3)

Kato TA, Monji A, Yasukawa K et al (2011) Aripiprazole inhibits superoxide generation from phorbol-myristate-acetate (PMA)-stimulated microglia in vitro: implication for antioxidative psychotropic actions via microglia. Schizophr Res, Jul 129:172-82.

Keegna DL, Rajupt AH (1973) Drug induced dystonia tarda: treatment with L-dopa. Dis Nerv Syst, Mar 34:167-9.

Mailman RB, Murthy V (2010) Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? Curr Pharm Des 16:488–501.

Mendhekar DN, Andrade C (2011) Prochlorperazine-induced tardive dystonia and its worsening with clozapine in a non-mentally ill patient with migraine. Ann. Pharmacother 45:545–6

Moghaddam B, Bunney BS (1990) Acute effects of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: an in vivo microdialysis study. J Neurochem 54:1755–60.

Molho ES, Factor SA (1999) Possible tardive dystonia resulting from clozapine therapy. Movement disorders 4:873-4.

Oommen E, Chand PK, Sharma PS (2006) Aripiprazole-induced tardive dystonia. Prim Care Companion J Clin Psychiatry 8:378-9.

Remington GJ (1988) The Pisa syndrome: possible role for serotonin and noradrenaline. J Clin Psychopharmacol 8:228–9.14.

Richelson E (1999) Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatr 60 (Suppl. 10) 5–14

Ryu S, Yoo JH, Kim JH, et al (2015) Tardive dyskinesia and tardive dystonia with second-generation antipsychotics in non-elderly schizophrenic patients unexposed to first-generation antipsychotics: a cross-sectional and retrospective study. J Clin Psychopharmacol Feb:35:13-21.

Simpson GM (2000) The treatment of tardive dyskinesia and tardive dystonia. J Clin Psychiatry 61:39–44.

Trugman JM, Leadbetter R, Zalis ME, et al (1994) Treatment of severe axial tardive dystonia with clozapine: case report and hypothesis. Mov Disord 9:441–6.

Van Harten PN, Kahn RS (1999) Tardive dystonia. Schizophr Bull 25:741–8.