Psychiatria Danubina, 2014; Vol. 26, No. 4, pp 360-362 *Case report*

SUCCESSFUL ELECTROCONVULSIVE THERAPY AND IMPROVEMENT OF NEGATIVE SYMPTOMS IN REFRACTORY SCHIZOPHRENIA WITH CLOZAPINE-INDUCED SEIZURES: A CASE REPORT

Soyeon Park[1] & Mi-kyeong Lee[2]

[1]Department of Psychiatry, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea
[2]Department of Psychiatry, Jurye Jayeon Hospital, Pusan, Republic of Korea

received: 14.7.2014; revised: 30.9.2014; accepted: 5.10.2014

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INTRODUCTION

Clozapine has been found to be superior to traditional neuroleptics in the treatment of refractory schizophrenia (Kane et al. 1988). Because it is associated with rare but life-threatening side effects, including agranulocytosis, myocarditis, aspiration pneumonia, ileus, and weight gain (Nielsen et al. 2013, Young et al. 1998), it is typically only recommended to patients with prominent and persistent psychotic symptoms despite trials of at least two different types of antipsychotic medications (Kreyenbuhl et al. 2010).

Among its many side effects, clozapine lowers the seizure threshold. The risk of seizure increases with increasing dosage and rapid dose titration (Devinsky et al. 1991), and additional factors for seizure induction include pre-existing seizure disorders, neurological abnormalities, and the simultaneous use of epileptogenic medications (Toth & Frankenburg 1994).

In addition to clozapine, several recent studies and reviews have indicated that electroconvulsive therapy (ECT) may be used to effectively treat patients with treatment-refractory schizophrenia (Kho et al. 2004, Kreyenbuhl et al. 2010). However, earlier reports have shown that most (80%) of the patients had their first spontaneous seizure within 5 weeks of the initiation of ECT treatment (Devinsky & Duchowny 1983). For that reason, ECT in patients with a low seizure threshold is thought to be risky.

We describe a case in which ECT was safe and useful for a schizophrenia patient with treatment-refractory auditory hallucinations who had clozapine-induced seizures.

CASE REPORT

Ms. P. was a 26-year-old woman who presented with auditory hallucinations and delusions of reference in June of 2008 and was diagnosed with schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) at another institute. This patient had no history of seizures or head trauma and a negative family history of psychiatric disorders. She started treatment with a combination of 30 mg/d olanzapine and 400 mg/d quetiapine for 3 months in 2008. She stopped taking the medication of her own volition in September of 2008 but maintained full remission for a year.

She presented with persistent psychotic symptoms again in 2009 and restarted the treatment at several hospitals. She took the previously prescribed medications again, but the combination was ineffective against her auditory hallucinations. Other trials of different psychiatric medications, including risperidone, paliperidone, and amisulpride, failed to attenuate her psychotic symptoms. She was switched to clozapine in June of 2013 by a psychiatrist who practiced outside of our institution. She started taking 50 mg of clozapine, which was increased to 450 mg for 4 months. We checked her complete blood counts regularly, which remained within normal ranges. She suffered from hallucinations intermittently during this time period. She complained of excessive sedation and sialorrhea and was also on benztropine and propranolol at 1 and 20 mg/d, respectively.

After taking the 450 mg/d dose of clozapine for 2 months, this patient had a seizure episode that was characterized by loss of consciousness, generalized tonic-clonic (GTC) movements of the limbs, and tongue biting, which lasted for 30 seconds with a post-episode confusional state, which was witnessed by her friends. Despite a reduction in her dose to 300 mg of clozapine, she experienced another GTC type-seizure episode that lasted for 2 minutes. After the episode, her medication was discontinued. She received first aid in an emergency room at another hospital, and it was confirmed that she had no brain abnormalities via a computed tomography (CT) scan.

She was admitted to our hospital to be assessed for seizures and to receive bidirectional pulse ECT (SpECTrum5000QECT device, Mecta Corp., Tualatin (OR), US) in March of 2014. At that time, she was suffering from persistent auditory hallucinations and also presented with negative symptoms, such as anergia, affective flattening, avolition, and social withdrawal.

She spent most of her time with her mother at home and stopped interacting with her friends. The contents of the auditory hallucination were that her brother was in danger and would be harmed.

Her physical and neurological examinations were unremarkable. The results of the investigations that were performed to rule out other causes of seizures (brain CT scan, levels of serum electrolytes and fasting blood glucose, and renal and liver function tests) were normal. An electroencephalogram (EEG) that was performed 2 weeks after the last seizure episode showed mild diffuse cerebral dysfunction and no epileptiform discharge. The possibility that the seizures were associated with clozapine therapy was considered. The patient was started on 6 mg/d risperidone and 15 mg/d escitalopram and remains on these medications.

After the first ECT was performed, the patient reported that the frequency of her hallucinations had reduced by half. She received six ECT treatments, and the convulsion times during the treatments were 32, 50, 82, 35, 25, and 40 seconds, respectively (Table 1). After completing 6 sessions, the patient showed increased spontaneous verbal expression and interpersonal activities. Her auditory hallucinations were completely eliminated. Following consultation with a neurologist, she was prescribed 250 mg of valproate to address the risk of seizure and discharged.

She presented with auditory hallucinations intermittently at one week following discharge, but her negative symptoms, including alogia, social withdrawal, and affective flattening, significantly improved. The Positive and Negative Syndrome Scale (PANSS) total scores decreased from 83 (P/N/G scores of 15/34/34, respectively) at baseline to 50 (P/N/G scores of 11/14/25, respectively) at the follow-up. The improvement of her negative PANSS symptoms was stronger than that of her positive PANSS symptoms. This patient attends regular follow-up visits and has remained seizure-free without any anticonvulsant therapy during the 4 month follow-up period.

DISCUSSION

We report the case of a patient with clozapine-induced seizures who was successfully treated with ECT. In this case, there was a clear improvement in her mood and negative symptoms in addition to her auditory hallucinations. Some studies have found that ECT improves positive symptoms but not negative symptoms (Chanpattana & Andrade 2006, Chanpattana & Sackeim 2010, Ucok & Cakr 2006). Others have shown that it is equally effective on both positive and negative symptoms (Kho et al. 2004). Although she had taken escitalopram, the rapid improvement of the patient's negative symptoms after ECT suggests that ECT, not the medication, was responsible for her improvement

Clozapine lowers the seizure threshold, and a dose-dependent risk of seizures is seen, particularly for doses of greater than 600 mg per day (Devinsky et al. 1991). The experiencing of a clozapine-induced seizure is not an absolute contraindication to continued treatment (Young et al. 1998). In one study, 78% of the patients who experienced seizures were successfully able to continue treatment with clozapine after a dose reduction, more gradual dose titration, or the addition of an anticonvulsant (Pacia & Devinsky 1994).

ECT can reduce the frequency of breakthrough spontaneous seizures in patients with epilepsy that are inadequately responsive to antiepileptic medication regimens (Shah et al. 2012). In another recent study, ECT was not found to cause epilepsy, and it was hypothesized that the patient's underlying organic condition may have influenced the development of seizures (Ray 2013). In the field of psychiatry, ECT is known to raise the seizure threshold in depressed patients (Fink et al. 1999, Sackeim 1999).

Therefore, the use of ECT has been demonstrated to be an effective and more affordable option for the treatment of schizophrenia with clozapine-induced seizures. This is a safe and effective strategy for the treatment of schizophrenia with a high risk of seizures.

Table 1. Details of electroconvulsive therapy program

Number	ECT Date	PW (ms)	Freq (Hz)	C (mC)	Energy (J)	Seizure Duration (s)	Anaesthetic	Side Effects
1	March, 10	1.40	60	117	18.7	38	Thiopental sodium	-
2	March, 12	1.40	60	117	28.9	50	Thiopental sodium	-
3	March, 17	1.40	60	117	19.9	82	Thiopental sodium	delirium
4	March, 19	1.40	50	73	13.3	35	Thiopental sodium	-
5	March, 21	1.40	50	50	7.8	25	Thiopental sodium	-
6	March, 24	1.40	40	42	6.2	40	Thiopental sodium	headache

PW= pulse width; Freq= frequency; C= stimulus charge

CONCLUSION

We report a case of a patient with clozapine-induced seizures who was successfully treated with ECT. In this case, there was a remarkable improvement in her mood and negative symptoms in addition to her auditory hallucinations. ECT can be a safe and effective strategy for schizophrenia patients with high seizure risks, including clozapine-related seizures.

Acknowledgements: None.

Conflict of interest: None to declare.

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Correspondence:
Soyeon Park, MD
Department of Psychiatry, University of Ulsan College of Medicine, Asan Medical Center
88 Olympic-ro 43-gil, Songpa-gu, Seoul 136-736, Republic of Korea
E-mail: soy0119@gmail.com